104

CHOLESTEROL MEASUREMENT: ERROR AND VARIABILITY

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Cholesterol Measurement: Error and...

ARING

BEFORE THE

SUBCOMMITTEE ON TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE

U.S. HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTH CONGRESS

FIRST SESSION

FEBRUARY 14, 1995

[No. 4]

Printed for the use of the Committee on Science

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*Ranking Minority Member
**Vice Chairman

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CHOLESTEROL MEASUREMENT: ERROR AND VARIABILITY

TUESDAY, FEBRUARY 14, 1995

U.S. HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE,
SUBCOMMITTEE ON TECHNOLOGY,
Washington, D. C.

The subcommittee met, pursuant to call, at 1:05 p.m. in Room 2318 of the Rayburn House Office Building, the Honorable Constance A. Morella, chairwoman of the subcommittee, presiding.

Mrs. MORELLA. I think we will start now.

It is a great pleasure to convene our first meeting of the Subcommittee on Technology of the House Science Committee.

It isn't official yet, but we have some reason to believe that this is the first Congressional committee or subcommittee in the history of the House of Representatives comprised of a majority of women.

I am excited about that, given the context especially of 48 out of 435 Members in the House, but I am also very excited about the issues that will be coming before our subcommittee during this Congress.

Technology lies close to the heart of everything that we do and offers all of us a more prosperous and bountiful future. Technology offers us much promise. The promise of a safer and cleaner environment; the promise of more profitable and competitive industries; the promise of a more informed, better educated, and healthier citizenry. Realizing these promises is the important work to which we will all be dedicating ourselves.

This subcommittee has a distinguished history of exercising jurisdiction whenever technology or technological research has had an impact on the lives, the health, or the prosperity of the American people. And I can't think of a more interesting or important topic than the one before us today: the accuracy of cholesterol measurement.

This is especially true today, on Valentine's Day, when I am sure that most Americans are paying attention to the hearts they have, and the hearts that they want to keep.

Today's hearing grows out of the work conducted by the former Investigations and Oversight Subcommittee on which I served as the Ranking Member in the past Congress.

We owe a debt of gratitude to the two former chairmen who helped to make this hearing possible today. I am speaking of my former colleague, Howard Wolpe, who as Chairman of the Investigations and Oversight Subcommittee of the House Science, Space, and Technology Committee, initiated the General Accounting Office studies on cholesterol, and also our former Chairman Jimmy Hayes, who sustained and guided these studies over the course of the past Congress when I served as Ranking Minority on that subcommittee. My thanks go out to both of them.

The subject of cholesterol and health is not a simple one. We will certainly not hear the last word on it today. The GAO study that is being released today is the first of three that are planned.

A second study, due out in a few months, will look at the scientific basis of the National Cholesterol Education Program, or NCEP as it is called in abbreviated form.

A third study will examine the effects of cholesterol programs on the medical, pharmaceutical, and food industries.

But today's hearing will be the first in a series of hearings that we do plan on this subject. Its purpose is not to force conclusions on cholesterol testing, the procedures for its testing, or its testing methodology.

This subcommittee intends to further pursue this matter when the GAO releases its follow-up report in May. At that time, we can make appropriate recommendations and suggestions based on additional findings to the American people.

I have reviewed this first study of the GAO on cholesterol measurement accuracy and variability with great interest, as have many others.

Heart disease is one of the leading killers in America today. Heart disease claims more than half a million lives every year and it costs society in excess of $50 billion annually.

High levels of serum cholesterol are correlated with an increased risk of coronary heart disease, and some two-thirds of American adults have had their cholesterol tested at some time over the past five years.

About 15 percent of people are modifying their diets in an effort to combat cholesterol, and some 4 to 5 million people are receiving cholesterol- lowering medications.

The total cost of cholesterol tests, treatments, diets, and programs may exceed, it is estimated, $10 billion annually.

The American public indeed has every right to inquire whether this is money that is well spent, and the public has the right to know whether it is being provided with health information that is accurate, useful, and reliable.

I look forward to having some of these questions answered here today. I want to thank our very able and learned panelists for testifying today.

I want now to recognize the distinguished Ranking Member of this subcommittee, Mr. Tanner, for any opening remarks that he may have.

[The prepared statement of Mrs. Morella follows:]

Chairwoman Connie Morella
Technology Subcommittee
Cholesterol Measurement Hearing
Opening Statement
February 14, 1995

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The American public has every right to inquire whether this is money well spent, and the public has a right to know whether it is being provided with health information that is accurate, useful, and reliable.

I look forward to having some of those questions answered here today. I thank our very learned and able panelists for testifying today, and I now recognize the distinguished Ranking Minority Member, Mr. Tanner, for any opening remarks he would like to offer.

Mr. TANNER. Thank you very much, Madam Chairwoman.

I want to thank you for holding this hearing today. It is a matter of great public interest, and it is one that is a very important issue as we survey the entire range of health delivery in the country.

As you suggested, the timing is particularly important since it is Valentine's Day, and there's chocolate candy and everything else around here today; cholesterol is a highly topical subject.

Cholesterol, fat, diet, and heart disease have become watchwords that are linked in the minds of Americans. The National Cholesterol Education Program has been extraordinarily successful in alerting the American public to the relationship between fat intake, cholesterol, and coronary heart disease.

We hear about cholesterol almost every day. For example, in the local Memphis paper in Tennessee, The Commercial Appeal, there were 147 articles on cholesterol during the last 12 months alone.

For millions of Americans, reduced fat, low-fat, non-fat, and steamed broccoli have become a way of life. Cholesterol monitoring, treatment, and diet is a multi-billion business.

We know for example that four to five million Americans are receiving cholesterol-lowering drugs, and as much as 15 percent of our population is practicing some form of dietary modification. So we are talking about very large numbers of people.

While the campaign to "know your number" on cholesterol is an important step toward increasing public awareness of the role cholesterol can play in heart disease, this GAO report today reminds us that it is almost impossible for individuals to know their cholesterol level based on a single measurement.

Biological and measuring device variations make this virtually impossible. What this report does suggest is that people need to be educated about how to be smart consumers of medical guidance; to ask the right questions, and to understand the test's limitations that are performed in the field of cholesterol monitoring.

As the Chairlady said, this series of GAO reports was initiated some two Congresses ago under Representative Howard Wolpe's chairmanship. I was pleased to be on the subcommittee then. Jimmy Hayes, as she noted, continued it last time, and so we are here today to receive this first GAO study focusing on the measurement of cholesterol, to be followed, as Mrs. Morella said, with two others.

I hope, and I know, this hearing today will be a useful piece of information for the American public to underscore the variances inherent in [1] the equipment used to measure cholesterol; [2] the techniques used to obtain the measure; and finally, the variation—biological, dietary, and otherwise—affecting a single measurement.

I look forward, Madam Chairwoman, to working with you on this very important subject and again want to commend you for having this hearing today.

[The prepared statement of Mr. Tanner follows:]

Opening Statement

The Honorable John S. Tanner (D-TN)

Ranking Member, Subcommittee on Technology
Committee on Science
U.S. House of Representatives

Cholesterol Measurement: Error and Variability

February 14, 1995

I am pleased to be here today and want to thank Chairwoman Morella for holding this very important hearing on the issue of cholesterol measurement variability. The timing of the hearing is particularly appropriate as the chocolates flow tonight.

Cholesterol, fat, diet, and heart disease have become watchwords that are inextricably linked in the minds of Americans. The National Cholesterol Education Program has been extraordinarily successful in alerting the American public about the relationship between fat, cholesterol, and coronary heart disease. We hear about cholesterol everywhere. In the local Memphis paper in my district, *The Commercial Appeal*, there were 147 articles on cholesterol during the past 12 months alone. For millions of Americans, reduced-fat, low-fat, non-fat, and steamed broccoli have become a way of life. Cholesterol monitoring, treatment, and diet has become a multi-billion dollar business. We know that 4-5 million Americans are receiving cholesterol lowering drugs and as much as 15% of our population is practicing some form of dietary modification. So we're talking about very large numbers of people.

While the National Cholesterol Education Program's campaign to "know your number" is an important step toward increasing public awareness of the role cholesterol plays in heart disease, this GAO report reminds us that it is almost impossible for individuals to know their cholesterol level based on a single measurement. Day-to-day variations from biological and behavioral factors and measurement device error make this impossible.

Currently there are 40 manufacturers who produce about 160 medical devices to measure cholesterol. GAO notes, "Studies show that under controlled conditions, particularly research, clinical, and hospital laboratories, measurement is reasonably accurate and precise. Considerably less is known, though, about the performance of cholesterol measurement in other settings, such as physicians' office laboratories and public health screenings." The GAO report continues, "Even if a single cholesterol measurement were analytically accurate and precise, it would not reflect how a person's cholesterol can vary from day to day." Cholesterol variation is also the result of normal biological fluctuations in a person's cholesterol level.

What this report does suggest is that people need to be educated about how to be smart "consumers" of medical guidance; to ask the right questions and understand the tests, and their limitations, that are performed for cholesterol monitoring.

This series of GAO reports was initiated by Representative Howard Wolpe (D-MI), Chairman of the Investigations and Oversight Subcommittee, Committee on Science, Space, and Technology, in the 102nd Congress. It was continued under Representative Jimmy Hayes (D-LA), Chairman of the Investigations and Oversight Subcommittee in the 103rd Congress.

This first GAO study focusing on the measurement of cholesterol, will be followed by a second report reviewing the findings of clinical trials used to support the recommendations of the National Cholesterol Education

Program. The final report will look at the National Cholesterol Education Program and its impact on the health and food industries.

This hearing will be useful piece of information to underscore the variances inherent in: 1.) the equipment used to measure cholesterol, 2.) the techniques used to obtain the measure, and 3) the variation -- biological, dietary, and otherwise, affecting a single measurement. This is a matter of great public interest.

I was a Member of the Investigations and Oversight Subcommittee when this work was initiated and I look forward to working with Chairwoman Morella as this work becomes available to our citizens.

Mrs. MORELLA. Thank you very much, Congressman Tanner. I appreciated your comments and your strong involvement in this issue on this subcommittee.

I would like to now give other Members an opportunity for any opening statements they might like to give, and I wanted to recognize them in the order in which people came.

First of all, one of our new Members of the committee, Congresswoman Barbara Cubin, who is from Wyoming.

Mrs. CUBIN. Thank you, Madam Chairwoman.

I simply want to thank you also for having this hearing. I have a professional interest in this subject, having worked in a medical office for 20 years, and my husband is a physician who treats heart attack patients.

Additionally, I have a strong family history of heart disease. So personally and professionally I appreciate the opportunity to learn something about this, and look forward to the testimony.

Mrs. MORELLA. Thank you, very much. You do indeed come with a great deal of experience.

Part of what we may hear may have to do with what doctors need to do more of.

I would now like to recognize Ms. McCarthy from Missouri.

Ms. MCCARTHY. Thank you, Madam Chairman. I will be brief.

I look forward to this hearing. I know this is an issue of great concern to the American public and will be of great value to us in the Congress as well.

Thank you very much.

Mrs. MORELLA. Thank you.

Ms. McCarthy comes from having chaired the National Conference of State Legislatures.

Mr. Gutknecht is here from Minnesota and I would like to recognize him.

Mr. GUTKNECHT. Thank you, Madam Chair. I will be even briefer.

One of my favorite expressions is "facts" and I look forward to hearing more facts and how effective some of the treatment is.

Mrs. MORELLA. You can notice how this Congress is one that is moving for action rather than rhetoric.

I would like to now recognize Mr. McHale who was on the committee in the last Congress, too, as a matter of fact, from Virginia—from Pennsylvania.

Mr. MCHALE. Madam Chair, in the continuing conflict between facts and stubborn matters, I am not sure which is more prevalent here on the Hill, but I would echo the words of my colleagues both in my family and in my district.

I have been touched by heart disease. My mother had a longstanding history of heart disease that ultimately took her life.

Many of my constituents raised the same questions that have been raised in my own family, and so I look forward to hearing the facts today from our witnesses in a hope that we can convert their contribution into meaningful legislation at some point in the not-too-distant-future.

Thank you.

Mrs. MORELLA. Thank you very much, Mr. McHale.

I would now like to recognize Congresswoman Eddie Bernice Johnson from Texas who also served on this committee in the last Congress.

Ms. JOHNSON. Thank you very much, Ms. Chairman.

I am grateful to you for having these hearings. Being of the few health professionals in the Congress, obviously I am very, very interested in health prevention.

Clearly every family has been touched by heart disease, kidney disease from the effects of cholesterol, and what we really need after reviewing this report is some accuracy in the testing.

I must hasten to say that all the tests that have been attempted are appreciated, and the progress which we have made has been noted and we see the effects; but obviously there is room for improvement, as there always is.

I hope that out of these hearings we will learn a lot and determine perhaps some recommended directions. Because since all of us have come to understand that health care is very costly, but it is much less costly when everyone is involved in their own care and being responsible for their own conditions, and fitness.

We are a Nation now that is aware of fitness. When we have tests, we want to know that the results that we get can be depended upon.

So I thank you very much.

Mrs. MORELLA. Thank you very much, Congresswoman Johnson.

I would now like to recognize another new Member to this Congress, someone we welcome, Congresswoman Andrea Seastrand from California.

Mrs. SEASTRAND. Well, thank you very much.

I am looking forward to hearing the experts. I know people throughout this Nation look to Congress and the 435 Members of the House look to the experts. In all the hearings that I have been participating in now from the Transportation Committee on to the Science Committee, I am overwhelmed and humbled by the experts coming before us with information.

So I am looking forward to learning more. I would say that my husband died of cancer. He had an excellent cholesterol number, but he died of cancer.

I come here as a layman wanting to learn more. We were on a journey with cancer for seven and a half years, so I come here as one, I say, who is a layman but who has been involved very much in fighting another disease.

So I am interested to learn all that I can from the gentleman and the ladies that testify today.

Thank you, very much.

Mrs. MORELLA. Thank you, very much.

So you can see how important this subject is in that coronary heart disease is the number one killer of men as well as women in the United States.

So let me ask our panelists to come forward and sit at the table to testify.

I will just briefly introduce that we have with us as witnesses Mr. Kwai-Cheung Chan. Mr. Chan is the Director of Program Evaluation in Physical Systems Areas of the U.S. General Accounting

Office. As a matter of fact, he is one who was very instrumental in this report, and he is going to explain it.

He is accompanied by John Oppenheim—I didn't know whether you wanted to sit up at the table, or not?

I want to also mention Philip Pierre who has been very much involved, also, in the GAO response and evaluation.

Also, Dr. Claude Lenfant. I was with Dr. Lenfant yesterday morning at the National Institutes of Health. He is the Director of the National Heart, Lung, and Blood Institute at the National Institutes of Health.

So as we start off, we will start off with the General Accounting Office report, and Mr. Chan.

Thank you.

STATEMENT OF MR. KWAI-CHEUNG CHAN, DIRECTOR OF PROGRAM EVALUATION IN PHYSICAL SYSTEMS AREAS, U.S. GENERAL ACCOUNTING OFFICE, WASHINGTON, D.C. ACCOMPANIED BY: MR. JOHN E. OPPENHEIM

Mr. CHAN. Good afternoon. Madam Chairwoman and Members of the Subcommittee. It is a pleasure to share with you the results of our recent study in which we examined how cholesterol is measured, and assessed what is known about the accuracy of different measurements.

The NIH established the NCEP in 1985 to [1] identify and treat individuals who are particularly at high risk; and [2] to get the entire population to reduce its cholesterol by encouraging people to "know their number" and modify their diet.

NCEP has issued adult treatment guidelines that emphasize classification and treatment decisions to be based on a person's risk status, which includes both an assessment of cholesterol levels—which are total cholesterol, HDL and LDL cholesterol—as well as other coronary heart disease risk factors.

These risk factors include things such as hypertension, smoking, obesity, physical inactivity, diabetes, as well as other non-socalled modifiable factors such as age, male, as well as family history of premature coronary heart disease.

It is estimated that about 30 percent of the American adults, or 52 million people, are candidates for dietary therapy. Of this group, some 13 million have cholesterol levels sufficiently high or elevated that they might be candidates for drug treatment.

Given the central role that cholesterol measurements have in classifying, evaluating, and treating individuals, having accurate measurements is important.

To address measurement variability, NCEP has established the goal that by 1992 a single total cholesterol measurement should be accurate within 8.9 percent. For the past 3 years, NCEP has also been attempting to set accuracy goals for HDL and LDL. These goals are expected to be issued shortly.

Now let me turn to our principal findings.

One. On measurement methods and analyzers:

Cholesterol tests are performed in many types of settings that include clinical, research, hospital, and physician office laboratories, as well as public screenings such as health fairs. Some 45 manufacturers have as many as 160 analyzers on the market that use different technologies as well as chemical formulations.

Although there are over 150,000 laboratories in the country that conduct medical tests—of which 60 percent are physician office laboratories—no national data area available on the number of these laboratories that do cholesterol tests or the number of tests that are done each year.

However, two-thirds of American adults have reported having had a cholesterol test in the last five years.

Of the different cholesterol components, the total cholesterol is the best understood and documented. And I will get into those later. In practice, LDL cholesterol has most often been calculated indirectly from measurements of total and HDL cholesterol as well as triglycerides. Because measuring LDL cholesterol relies on the accuracy of these other measurements, potential measurement error can be greatly compounded.

Unfortunately, I am unable to explain through that process which I call "classification measurement," as well as ultimately what leads to either dietary or drug intervention. We made some copies to pass around to show you so you can see it better.

What I would like you to focus on is that essentially every step that is taken is determined by the fact that we do have some measurement. When we have the measurement, we go to the next step to make some decisions. As a result, we ask for other factors such as risk factors that were discussed earlier that get introduced in that decision making process.

What you can see to the very end of this is that the last step you have is drug therapy, to your right lower-hand corner. Although half of the American people, and particularly adults, really do not have over 200 milligrams per deciliter in their total cholesterol, so in fact all they do is end up in the so-called "risk advice" level. The rest sort of filter through.

So you can see this is sort of like a flow diagram as you move from one point to the next in the decision being made about which steps need to be taken.

Basically what you can see from this diagram is we have on the left-hand side the desirable total cholesterol. At the next level you see HDL, which is the high density lipid as the measurement requirement. Then you move to almost the center and you see three boxes, which is "desirable LDL," "borderline high risk LDL" as well as "high risk LDL." So that is what I am going to concentrate on in this discussion.

Let's go back to our principal findings.

Number two, on measurement accuracy of analyzers.

With no overall evaluation of different instruments and laboratories having been conducted, it is not possible to know whether the accuracy goals established in 1992 for cholesterol measurement have been met.

A number of studies show that under controlled conditions, particularly research, clinical, and hospital laboratories, measurement of patient specimens is reasonably accurate. However, measurement problems have been found when accuracy was evaluated with processed reference materials which tend to react differently from patient specimens. One major study, for example, found that 70 percent of the instruments tested were subject to these effects, thus hampering efforts to monitor and assess accuracy.

Much less is known about the performance of cholesterol measurement in settings such as the physicians' office laboratories—and as I stated before, there are about 60 percent of these labs that are in physicians' offices—as well as public screenings where many people are routinely tested.

Many of the portable desk-top analyzers which are used in these settings can provide fairly accurate measurements if they are appropriately maintained. However, studies showed that several of these instruments have not met the established goals for accuracy and incorrectly overestimated or underestimated from 17 percent to 50 percent of patient samples.

Number three, on factors that influence cholesterol levels:

Aside from instrument variability, an individual's own cholesterol level can vary over time. Some variation is normal and is expected because of inherent biological factors. These factors may account for up to 65 percent of the total variation in an individual's reported cholesterol measurement—which means the other 35 percent is really the analytical side, which is the instrument measurement problems. The average amount of biological variation is estimated to be 6.1 percent for total cholesterol, 7.4 percent for HDL, and 9.5 percent for LDL.

Biological factors stem from "behavioral" factors such as diet, exercise, and alcohol consumption, as well as from "clinical" factors such as illness, medications, and pregnancy.

One study estimated that 4 to 6 percent of the variance in HDL cholesterol levels in the population may be linked to alcohol consumption.

A different study on exercise showed that previously sedentary patients who undertook brisk walking decreased their total cholesterol by 5 percent, and increased their HDL cholesterol by 25 percent.

The way blood specimens are collected and handled can also increase variability. For example, one study has reported that if you use finger-stick samples for total cholesterol, the result would be 7 percent higher than the venous samples when both were analyzed in the same testing instrument. That means if you take the blood from your finger versus from your vein, there is a difference in terms of results.

Even the length of time an individual is sitting or standing before taking the test demonstrated a chance in your cholesterol level.

Finally, on Potential Effect of Inaccurate Measurements:

The total error associated with both instrument and biological variability can be considerable. If we use the number of NCEP goal for instrument variability and the average biological variability derived from a synthesis of existing studies, the total error for a single measurement of total cholesterol would be about 16 percent.

For example, if someone received a value of 240 for their total cholesterol, the variation could be as low as 200 versus as high as 280. Similarly, a single measurement of HDL cholesterol with a value of 35 mg/dL could range from 24 to 46 mg/dL.

Although the NCEP guidelines acknowledge measurement variability and stress the need for multiple measurements, there is the possibility that important consequences can result from measurement error.

These could result in either [1] the treatment of individuals who in fact had desirable cholesterol levels; or [2] incorrectly reassuring an individual that his or her cholesterol level was desirable or acceptable.

The potential for misclassification could be greatest for those whose measurements are near the cutpoints that differentiate the risk categories, as shown in this flow diagram [indicating].

In summary, we found that instrument measurement error and variations from biological factors make it highly unlikely that an individual can "know" their cholesterol levels based on a single measurement.

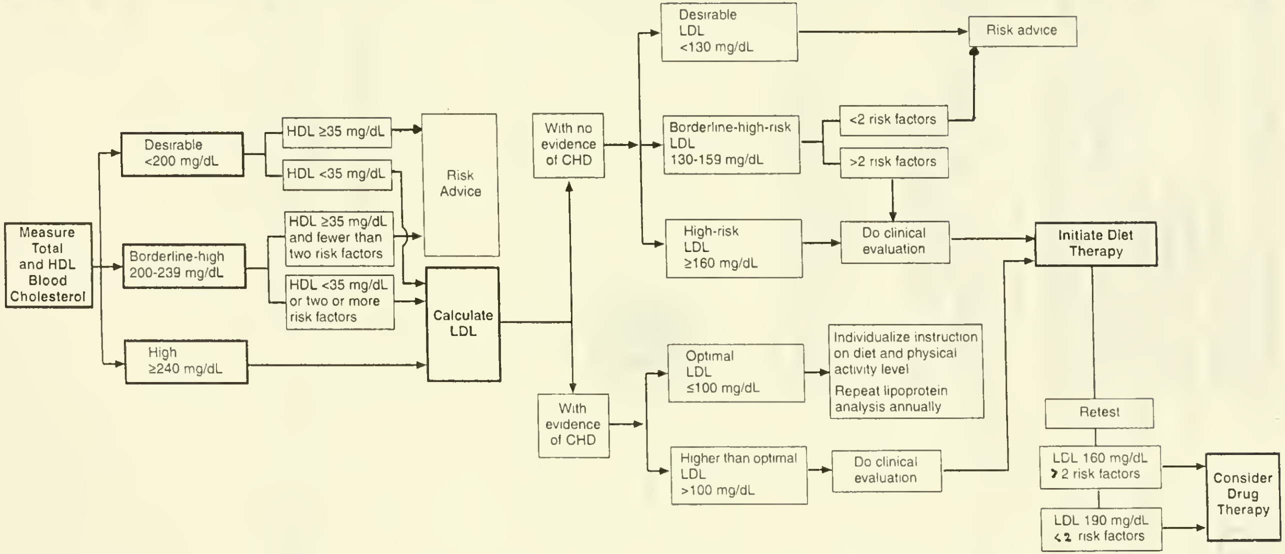
Because of such variation, cholesterol levels should be viewed in terms of ranges rather than as absolute fixed numbers. To minimize the potential for misclassification problems, it is important to ensure that physicians are knowledgeable about measurement variability and base their decisions on the average of multiple tests as well as an assessment of other risk factors all recommended by NCEP.

At the same time, continuing efforts are needed to improve the accuracy of cholesterol measurements so that medical decisions to initiate and continue treatment to lower elevated cholesterol can be both effective and efficient.

This concludes my statement. Thank you.

[The prepared statement of Mr. Chan follows:]

GAO Cholesterol Numbers Inform Prevention Advice and Treatment



Measure Total and HDL Blood Cholesterol

Desirable <200 mg/dL

Borderline-high 200-239 mg/dL

High ≥240 mg/dL

HDL ≥35 mg/dL

HDL <35 mg/dL

HDL ≥35 mg/dL and fewer than two risk factors

HDL <35 mg/dL or two or more risk factors

Risk Advice

Calculate LDL

With no evidence of CHD

With evidence of CHD

Desirable LDL <130 mg/dL

Borderline-high-risk LDL 130-159 mg/dL

High-risk LDL ≥160 mg/dL

Optimal LDL ≤100 mg/dL

Higher than optimal LDL >100 mg/dL

<2 risk factors

>2 risk factors

Risk advice

Do clinical evaluation

Individualize instruction on diet and physical activity level

Repeat lipoprotein analysis annually

Do clinical evaluation

Initiate Diet Therapy

Retest

LDL 160 mg/dL > 2 risk factors

LDL 190 mg/dL < 2 risk factors

Consider Drug Therapy

Source: "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," National Cholesterol Education Program, Bethesda, Maryland, 1993.

United States General Accounting Office

GAO

Testimony
Before the Subcommittee on Technology,
Committee on Science,
House of Representatives

For Release on
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CHOLESTEROL MEASUREMENT

Variability in Methods and Test Results

Statement of Kwai-Cheung Chan
Director of Program Evaluation in Physical Systems Areas
Program Evaluation and Methodology Division

Madam Chairman and Members of the Subcommittee:

It is a pleasure to share with you the results of a recent study in which we examined how cholesterol is measured in different laboratory settings and assessed what is known about the accuracy of different measurement techniques. My statement is based upon our study's report, entitled Cholesterol Measurement: Test Accuracy and Factors That Influence Cholesterol Levels, which is being issued today.

This work is one of three studies that the former Subcommittee on Investigations and Oversight asked us to conduct on the National Cholesterol Education Program (NCEP). The National Institutes of Health (NIH) established NCEP in 1985 to encourage Americans to lower their high blood cholesterol levels with the objective of reducing coronary heart disease. In one of the other studies, we are reviewing the findings of the clinical trials that have been used to support NCEP, and in the third, we plan to look into how NCEP has influenced the health and food industries.

Let me begin by briefly highlighting the key results of our cholesterol measurement study. In conducting this work, we synthesized a large body of relevant scientific literature and interviewed measurement experts who work in government agencies, private industry, universities, and clinical laboratories.

We found that instrument measurement error and day-to-day variations from biological and behavioral factors make it highly unlikely that individuals can "know" their cholesterol levels based on a single measurement. Because of such variation, cholesterol levels should be viewed in terms of ranges rather than as absolute fixed numbers. Individuals and physicians need to be aware of cholesterol measurement variability, and any decisions to classify patients and initiate treatment should be based on the average of multiple measurements as well as on an assessment of other risk factors, as recommended by NCEP's guidelines. This is particularly important when measured cholesterol levels are close to the cutpoints that differentiate risk categories and may lead to recommendations for treatment with drugs.

Although much progress has been made in developing better testing methods and materials in recent years, cholesterol continues to be difficult to measure with accuracy and consistency across the broad range of instruments and settings in which it is analyzed. Studies show that under controlled conditions, particularly research, clinical, and hospital laboratories, measurement is reasonably accurate. Considerably less is known, though, about the performance of cholesterol measurement in other settings, such as physicians' office laboratories and public health screenings, where many people are routinely tested. Since no overall evaluation of different instruments and laboratories has been conducted, it is impossible to know whether the accuracy goals established for cholesterol measurement have been met.

Furthermore, even if a laboratory is able to provide reasonably accurate test results, biological factors such as diet, exercise, and illness cause an individual's cholesterol level to vary. Some individuals' cholesterol levels can vary dramatically over time while others' remain relatively constant. Although some biological variation can be minimized, if individuals, maintain their weight and diet for a modest period prior to measurement, many other factors cannot be controlled for and reduced.

Before turning to any further discussion of our findings, let me first provide some background information on cholesterol and the NCEP guidelines.

BACKGROUND

Coronary heart disease is a leading cause of death for Americans, accounting for about half a million deaths per year. Further, about 1.25 million Americans suffer heart attacks each year. The American Heart Association estimates that total costs associated with coronary heart disease amount to about $55 billion per year. Because of the large numbers of people affected and the large costs involved, efforts have focused on prevention.

Within the federal government's effort to address the problem of heart disease, NIH has established several education programs to inform the public about different risk factors associated with heart disease and to provide guidelines for reducing risks that can be modified. The major factors that influence a person's chance (or risk) of getting coronary heart disease include high blood pressure, cigarette smoking, high blood cholesterol, diabetes, age (45 years or older for men; 55 years or older for women), family history of early heart disease, physical inactivity, and obesity.

Accumulated scientific evidence has shown that individuals with higher levels of blood cholesterol have a greater risk of coronary heart disease. Certain amounts of cholesterol, however, are essential to the body, helping form cell membranes and some hormones. Cholesterol is manufactured by the body (mostly in the liver) and derived from the diet (in foods containing cholesterol as well as those that are high in certain saturated fats).

Cholesterol is transported through the blood by carriers called lipoproteins. Of the several different kinds of lipoproteins, two are of major importance: low-density lipoprotein (LDL) and high-density lipoprotein (HDL). LDL cholesterol, which contains about 60 to 70 percent of the total cholesterol, is often referred to as the "bad" cholesterol because too much of it can cause a buildup of plaque in the arteries that can block the flow of blood and subsequently result in a heart attack. HDL cholesterol is believed to help remove excess cholesterol from the blood and prevent the buildup of plaque and is thus referred to as the "good" cholesterol. A higher level of LDL cholesterol is associated with a higher risk of heart disease, whereas a higher level of HDL cholesterol is associated with a lower risk of heart disease. LDL and HDL cholesterol levels, however, are considered independent risk factors with different determinants.

NCEP Treatment and Measurement Guidelines

NCEP emphasizes two parallel approaches to (1) identify and treat individuals who are particularly at high risk and (2) get the entire population to reduce its cholesterol by encouraging people to "know their cholesterol number" and modify their diet. NCEP convened expert panels and published adult treatment guidelines in 1988 and 1993, covering the classification of cholesterol, patient evaluation, and dietary and drug treatments.

These guidelines emphasize classification and treatment decisions based on a person's risk status, which is defined by cholesterol levels (including total, HDL, and LDL cholesterol) in conjunction with other key coronary heart disease risk factors. The guidelines recommend that all adults have their total cholesterol measured at least once every 5 years and that HDL cholesterol be measured at the same time. Individuals with high cholesterol and existing symptoms of coronary heart disease or at least two other heart disease risk factors are candidates for more intensive treatment.

NCEP classifies total cholesterol into three distinct levels: desirable (below 200 mg/dL), borderline high (200 to 239 mg/dL), and high (equal to or above 240 mg/dL). In addition, an HDL cholesterol level of less than 35 mg/dL is considered low and a contributing risk factor for coronary heart disease. Individuals without evidence of existing coronary heart disease are recommended to have a follow-up lipoprotein analysis if they have one of the following characteristics: (1) high total cholesterol, (2) borderline-high cholesterol and low HDL cholesterol, or (3) borderline-high cholesterol, higher HDL cholesterol, but two or more risk factors. Lipoprotein analysis includes measurement of fasting levels of total cholesterol, HDL cholesterol, and triglycerides and the calculation of LDL cholesterol.

NCEP also classifies LDL cholesterol into three levels: desirable (less than 130 mg/dL), borderline high risk (130 to 159 mg/dL), and high risk (equal to or greater than 160 mg/dL).

Decisions for beginning diet or drug treatment are based on these LDL levels in combination with other evident risk factors. Thus, candidates for diet therapy without existing symptoms of coronary heart disease include those with high LDL cholesterol (160 mg/dL or more) or those with borderline-high LDL cholesterol (130-159 mg/dL) plus two or more risk factors. NCEP recommends diet therapy as a first line of treatment for most individuals, with drugs to follow if the diet is ineffective at lowering LDL cholesterol. Individuals usually must maintain long-term treatment in order to keep their cholesterol at reduced levels.

Although national data indicate that cholesterol levels for the U.S. population have declined since the early 1960's, the average total serum cholesterol for adults is currently about 205 mg/dL (within NCEP's borderline-high category). Women tend to have lower total and LDL cholesterol levels than men up to the age of menopause, at which time they increase to levels slightly above those of men. Compared to men, women also appear to have higher HDL cholesterol levels. It is estimated that 29 percent of American adults--52 million people--are candidates for dietary therapy. Of this group, it is estimated that 12.7 million have cholesterol levels sufficiently elevated that they might be candidates for drug therapy.

For a widespread cholesterol-lowering campaign to be effective, it is important that individuals and physicians be able to obtain accurate test results. NCEP convened a panel of experts in 1988 who concluded that considerable inaccuracy in cholesterol testing existed in the United States. They and a subsequent panel in 1990 made recommendations about how cholesterol measurement could be standardized and improved.

Recognizing the problem of measurement variability, NCEP has recommended that two separate cholesterol measurements be averaged together to assess an individual's level, with a further test to be conducted if the first two varied substantially. They also established the goal that by 1992 a single total cholesterol measurement should be accurate within ±8.9 percent. NCEP has not previously issued goals for HDL and LDL cholesterol measurement, but such goals are expected to be issued shortly. The Health Care Financing Administration (HCFA) has also established testing requirements for total cholesterol (±10 percent) and HDL cholesterol (±30 percent).

With this background, we can now turn to some of our study findings.

PRINCIPAL FINDINGS

Measurement Methods and Analyzers

Currently, 45 manufacturers have as many as 160 device systems on the market that use different technologies and chemical formulations to conduct cholesterol tests in different settings. Cholesterol is commonly tested in clinical, research, hospital, and physician office laboratories as well as in mass screenings such as public health fairs. Although over 150,000 U.S. laboratories that conduct medical tests have registered with HCFA, under implementation of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), no national data are available on the number of laboratories that do cholesterol tests or the number of tests that are done each year.

Of the different cholesterol components, total cholesterol is the best understood and documented. HDL and LDL cholesterol, which have been given greater emphasis under the NCEP guidelines, are more difficult to measure. Officials we interviewed from the Centers for Disease Control and Prevention (CDC) pointed out that considerable scientific work remains before HDL measurement is as well understood as total cholesterol currently is. Direct measurement methods for LDL cholesterol have not generally been available in most cholesterol test settings, although such a method has recently been marketed. In practice, LDL cholesterol has usually been calculated from measurements of total cholesterol, HDL cholesterol, and triglycerides. Because measuring LDL cholesterol relies on the accuracy of these other measurements, potential measurement error can be greatly compounded.

Measurement Accuracy

A process to assess and improve cholesterol measurement was established under the National Reference System for Cholesterol. Rather than require that all laboratories use the same devices and test methods, emphasis is directed toward having test results consistent with accepted accuracy standards. CDC and the National Institute of Standards and Technology have developed reference methods as well as processed reference materials that device manufacturers and clinical laboratories can use to assess cholesterol measurement accuracy. As part of this system, CDC supports a network of nine reference laboratories in the United States. A laboratory can gauge its accuracy and standardize its measurements by splitting samples with a CDC network laboratory and comparing results. Participation in the network, however, has been relatively low according to CDC officials. In 1992, for example, 167 laboratories applied for a certificate of traceability to the CDC standards, and 79 percent passed.

Laboratories can also participate in proficiency testing programs such as those conducted by the College of American Pathologists (CAP) and the American Association of Bioanalysts. In these programs, participating laboratories receive, analyze, and compare results with processed reference materials that have an assigned target value for cholesterol. CAP, the largest such testing program, has 12,000 subscribers that use its service to evaluate several different clinical chemistry tests. In addition, under the CLIA implementation, HCFA has recently begun conducting laboratory inspections to assess quality control procedures and test results on all medical equipment, including cholesterol testing.

Survey data from CAP indicate that interlaboratory measurement variability (the extent to which test values varied from one laboratory to the next) for total cholesterol has improved over the past 40 years, declining from about 24 to 6 percent. Furthermore, several large collaborative studies of selected clinical laboratories have found that accuracy was good when testing was evaluated with patients' specimens. Measurement error problems occurred, however, when accuracy was evaluated using processed reference materials. Because such materials behave differently from fresh patient samples, they can produce different test results on many types of devices. Since such materials are an important component of proficiency testing programs, problems with them will hamper both standardization and government monitoring efforts.

Studies of portable desk-top analyzers, such as those used in physician offices and public health screenings, indicate that many of these devices can provide fairly accurate measurements when they are operated properly under controlled conditions. Studies, however, have also documented that several devices did not meet the established goals for accuracy, and incorrectly overestimated or underestimated from 17 to nearly 50 percent of patient samples, based on the NCEP risk categories.

Factors That Influence Cholesterol Levels

Although cholesterol testing methods and devices may be able to measure a sample of cholesterol accurately and reliably, a single test result does not reflect how an individual's cholesterol level can vary over time. Some variation in an individual's cholesterol level is normal and to be expected because of biological factors. It has been estimated that such factors may account for up to 65 percent of the total variation in an individual's reported cholesterol measurement. A recent synthesis of several studies found that biological variation in individuals averaged 6.1 percent for total cholesterol, 7.4 percent for HDL cholesterol, and 9.5 percent for LDL cholesterol.

Biological factors stem from behavioral influences such as diet, exercise, and alcohol consumption as well as from clinical factors such as illness, medications, and pregnancy. With diet, for example, changes in the consumption of foods high in saturated fats and cholesterol can raise or lower blood cholesterol levels, although individuals tend to respond quite differently to changes in diet. Similarly, exercise can alter cholesterol levels and cause measurement variability, depending on the volume, intensity, and type of exercise undertaken. Studies have also shown that total and LDL cholesterol levels within individuals tend to vary by season, being slightly higher in winter than summer.

In addition to biological factors, differences in the way blood specimens are collected and handled can lead to different results. Recent studies, for example, have reported that capillary (finger-stick) samples are more variable than venous samples, and researchers have called for more standardized capillary collection procedures. This finding is important because capillary specimens are taken in screening settings and are used in recently marketed home test kits. The knowledge and training of technicians who take and prepare blood specimens for analysis can also contribute to measurement variability. For example, the length of time an individual is sitting or standing before being tested has been demonstrated to influence cholesterol levels. In addition, the proper storage of specimens is important to avoid changes in the composition of the blood serum and to ensure accurate measurement results.

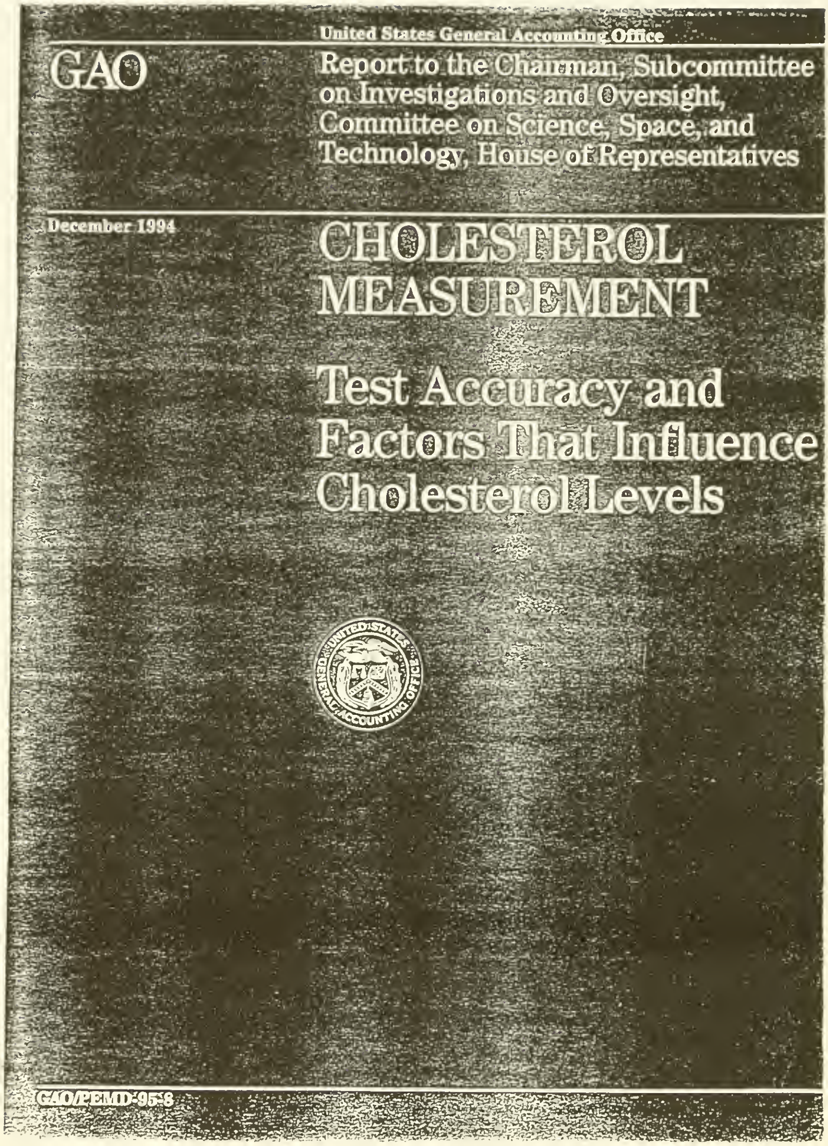
Potential Effect of Inaccurate Measurements

The total error associated with both instrument and biological variability can be considerable. If, for example, the total error for a single measurement of total cholesterol is assumed to be about 16 percent (which is equivalent to the sum of the NCEP goal for instrument variability plus the average biological variability derived from a synthesis of existing studies), then a value of 240 mg/dL could be expected to range from 201 to 279 mg/dL. Similarly, a single measurement of HDL cholesterol with a known value of 35 mg/dL could range from 24 to 46 mg/dL based on combined analytical and biological variability. Multiple measurements narrow the variability; however, some variability cannot be reduced since many factors that affect cholesterol measurement cannot be controlled.

Having accurate cholesterol measurements is important, given the central role that cholesterol cutpoints have in classifying, evaluating, and treating individuals deemed at risk of coronary heart disease. Although the NCEP guidelines acknowledge the issue of measurement variability and stress the need for multiple measurements, important consequences can result from measurement error. Some physicians may not consider measurement errors and may base their decisions on only a single measurement that may incorrectly characterize an individual's cholesterol level. In a worst-case scenario, two types of diagnostic errors could occur: (1) a false-positive error could result in the treatment of individuals with drugs who in fact had desirable cholesterol levels or (2) a false-negative error could incorrectly reassure an individual that his or her cholesterol level was desirable. The potential for misclassification would be greatest for those whose measurements are near the high-risk cutpoint.

Continuing efforts are needed to improve the accuracy of cholesterol measurements so that medical decisions to initiate and continue treatment to lower elevated cholesterol can be both effective and efficient. To minimize potential misclassification problems, it is also important to ensure that physicians are knowledgeable about measurement variability and the need to conduct multiple tests before initiating treatment.

Madam Chairman, this concludes my prepared statement. I would be happy to address any questions that you or members of the Subcommittee may have at this time.



United States General Accounting Office

GAO

Report to the Chairman, Subcommittee on Investigations and Oversight, Committee on Science, Space, and Technology, House of Representatives

December 1994

CHOLESTEROL MEASUREMENT

Test Accuracy and Factors That Influence Cholesterol Levels

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GAO
United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

B-257298

December 30, 1994

The Honorable James A. Hayes
Chairman, Subcommittee on Investigations
and Oversight
Committee on Science, Space, and
Technology
House of Representatives

Dear Mr. Chairman:

In response to your request, we are submitting this report, which examines how cholesterol an its subfractions are measured in different laboratory settings and discusses what is known about the accuracy of these measurement techniques. The report also discusses various analytical and biological factors that can affect an individual's cholesterol levels. Furthermore, the report assesses the potential effect of cholesterol measurement variability and the classification and treatment of patients.

We are sending copies to interested congressional committees and government agencies, and we will make copies available to others upon request. If you have any questions or would like additional information, please call me at (202) 512-2900 or Kwai-Cheung Chan, Director of Program Evaluation in Physical Systems Areas, at (202) 512-3092. Major contributors to this report are listed in appendix II.

Sincerely yours,

Terry E. Hedrick
Assistant Comptroller General

Executive Summary

Purpose

Coronary heart disease is a leading cause of death for Americans, and preventive measures have emphasized reducing risk factors such as high blood cholesterol levels. In 1985, the National Institutes of Health launched the National Cholesterol Education Program (NCEP) to encourage Americans to have their cholesterol measured and modify their diet and to provide clinical guidelines for identifying and treating persons who are particularly at high risk of heart disease. If such efforts are to be successful, they clearly require accurate cholesterol test results.

The Subcommittee on Investigations and Oversight of the House Committee on Science, Space, and Technology asked GAO to review several topics related to NCEP. Accordingly, this report addresses the following evaluation questions: (1) How is cholesterol measured? (2) What is known about the accuracy and precision of cholesterol measurement techniques? (3) What factors influence cholesterol levels? (4) What is the potential effect of uncertain measurement?

Background

Elevated levels of serum blood cholesterol have been shown to be positively correlated with increased rates of coronary heart disease. Certain amounts of cholesterol, however, are essential to the body, affecting the production of hormones and bile acids as well as being a structural component of cell membranes. Cholesterol is manufactured by the body and derived through the consumption of foods that contain cholesterol as well as those that are high in certain saturated fats.

The NCEP adult guidelines emphasize classification and treatment decisions based on a person's risk status, which is defined by serum cholesterol levels (including total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol) in conjunction with other coronary heart disease risk factors (such as high blood pressure or a family history of heart disease). Cholesterol measurement plays a central role in the classification of individuals into risk categories (desirable, borderline high, and high) and in monitoring the progress of patients being treated. The goal for treatment is to reduce LDL cholesterol, using diet as a first step and then cholesterol-lowering drugs if diet is not successful.

Although national data indicate that cholesterol levels for the U.S. population have declined since the early 1960's, the average total serum cholesterol for adults is currently about 205 mg/dL (slightly above NCEP's borderline-high category). It is estimated that 29 percent of American adults—52 million people—are candidates for dietary therapy. Of this group, 12.7 million are considered to need drug therapy, often a lifelong proposition.

An NCEP panel of experts in 1988 found considerable inaccuracy in cholesterol testing in the United States. They and a subsequent panel in 1990 made recommendations about how cholesterol measurement coul be standardized and improved. They recommended that two separate cholesterol measurements be averaged together to assess an individual' level, with a further test to be conducted if the first two varied substantially. The panels also established the goal that by 1992 a single total cholesterol measurement should be accurate within ±8.9 percent. T Health Care Financing Administration (HCFA) has also established testin requirements for total cholesterol (±10 percent) and HDL cholesterol (±30 percent).

To address the questions outlined above, GAO identified relevant scientifi literature published largely since 1988, integrated findings across studies and interviewed measurement experts who work in government agencie private industry, universities, and clinical laboratories.

Results in Brief

NCEP has encouraged Americans to know their cholesterol number, and i fact nearly two thirds of all adults have had a cholesterol test in the past years. Instrument measurement error and day-to-day variations from biological and behavioral factors make it highly unlikely that individuals can "know" their cholesterol levels based on a single measurement. Cholesterol levels should be viewed in terms of ranges rather than as absolute fixed numbers. It is important that individuals and physicians b aware of cholesterol measurement variability and that decisions to classi patients and initiate treatment be based on the average of multiple measurements and assessment of other risk factors, as recommended by the NCEP guidelines. This is particularly important when measured cholesterol levels are around the cutpoints that differentiate risk categories and may lead to recommendations for treatment with drugs.

Some progress has been made in improving analytical accuracy in cholesterol measurement, with the development of better methods and materials in recent years. Yet, cholesterol continues to be difficult to measure with accuracy and consistency across the broad range of device and settings in which it is analyzed. Studies show that under controlled conditions, particularly research, clinical, and hospital laboratories, measurement is reasonably accurate and precise. Considerably less is known, though, about the performance of cholesterol measurement in other settings, such as physicians' office laboratories and public health screenings. Since no overall evaluation of different instruments and laboratories has been conducted, it is impossible to know whether the accuracy goals established for total and HDL cholesterol have been or could be met.

Even if a laboratory could provide reasonably accurate and precise test results, biological and behavioral factors such as diet, exercise, and illness cause an individual's cholesterol level to vary. It has been estimated that such factors may account for up to 65 percent of total variation. Studies have documented that some individuals' cholesterol levels can vary dramatically from week to week while others' remain relatively constant. Although some biological variation can be controlled for, by having individuals maintain their weight and diet for a modest period prior to measurement, many factors cannot be controlled.

Principal Findings

Measurement Methods and Analyzers

Currently, over 40 manufacturers have as many as 160 device systems on the market that use different technologies and chemical formulations to conduct cholesterol tests in different settings, making it difficult to standardize measurement. Although HCFA has registered over 150,000 U.S. laboratories that conduct medical tests, GAO could not ascertain the number of laboratories that do cholesterol tests or the number of tests that are done each year. Under the requirements of the Clinical Laboratory Improvement Amendments of 1988, HCFA has recently begun conducting laboratory inspections to assess quality control procedures and test results on all medical equipment, including cholesterol testing.

Accuracy and Precision

A process to assess and improve cholesterol measurement was established under the National Reference System for Cholesterol. Rather than require that all laboratories use the same devices and test methods, emphasis is directed toward having test results consistent with accepted accuracy standards. The Centers for Disease Control and Prevention and the National Institute of Standards and Technology have developed reference methods as well as quality control testing materials that some device manufacturers and clinical laboratories have used to assess cholesterol measurement accuracy. In addition, laboratories can participate in proficiency testing programs.

Survey data from the College of American Pathologists indicate that laboratory measurement precision for total cholesterol has improved from about 25 to 6 percent error. While several large collaborative studies of selected clinical laboratories have found that accuracy was good for patients' specimens, measurement error problems occurred when accuracy was evaluated using processed quality control materials. Because such materials behave differently from fresh patient samples and are an important component of proficiency testing programs, problems with them will severely hamper both standardization and government monitoring efforts.

Studies of desk-top analyzers have found accuracy problems for total and HDL measurements. Several devices did not meet established goals for accuracy, and estimated misclassification rates for some devices ranged from 17 to nearly 50 percent. Currently, the NCEP guidelines place a great deal of emphasis on the importance of HDL and LDL cholesterol as risk factors, which are considerably more difficult to measure than total cholesterol. LDL is usually calculated with a formula that uses measures of total cholesterol, HDL cholesterol, and triglycerides. Because the formula relies on the accuracy of these other measures, LDL measurement error can be greatly compounded.

Factors That Influence Cholesterol Levels

Some variation in an individual's total, HDL, and LDL cholesterol is normal and to be expected. A recent synthesis of several studies found that the average biological variation of total cholesterol is 6.1 percent, HDL cholesterol 7.4 percent, and LDL cholesterol 9.5 percent. Biological variation stems from behavioral factors such as diet, exercise, and alcohol consumption and clinical factors such as illness, medications, and pregnancy. Changes in the consumption of saturated fats and cholesterol raise or lower serum cholesterol levels, although individuals tend to respond quite differently to changes in diet. The extent of the effect on cholesterol levels varies depending on the amount of food intake and exercise and biological factors.

In addition, differences in the way blood specimens are collected and handled can have different results. Recent studies, for example, have reported that capillary (finger-stick) samples are more variable than venous samples, and researchers have called for more-standardized capillary collection procedures. This finding is important because capilla specimens are taken in screening settings and are used in recently approved and marketed home test kits.

Potential Effect of Inaccurate Measurements

The total error associated with analytical and biological variability can have important consequences. If, for example, the total error is assumed be 16 percent (equivalent to the sum of the NCEP goal for analytical variability plus the average biological variability derived from a synthesis of existing studies), then a single measurement of total cholesterol with a known value of 240 mg/dL could be expected to range from 201 to 279 mg/dL. Similarly, a single measurement of HDL cholesterol with a known value of 35 mg/dL could range from 24 to 46 mg/dL based on analytical a biological variability. Multiple measurements narrow the variability; however, some variability cannot be reduced since many factors that affect cholesterol measurement cannot be controlled.

In a worst-case scenario, two types of diagnostic errors could occur if physicians do not account for measurement problems and base classification and treatment decisions on only a single measurement. A false-positive error could result in the treatment of individuals with drug who in fact had desirable cholesterol levels. A false-negative error could result in incorrectly reassuring an individual that his or her cholesterol level was desirable. The potential for misclassification would be greatest for those who are near a high-risk cutpoint.

Recommendations

GAO is making no recommendations in this report.

Agency Comments

Officials from the Department of Health and Human Services reviewed a draft of this report and provided written comments (see appendix I). GAO incorporated many of the technical comments they provided in the text where appropriate. Overall, they believed that the state of cholesterol accuracy across the country is better than what is reflected in the draft report. However, they also acknowledged the need for better standardization materials to assess accuracy.

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Abbreviations

AHA	American Heart Association
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
GAO	General Accounting Office
HCFA	Health Care Financing Administration
HDL	High-density lipoprotein
HHS	Department of Health and Human Services
LDL	Low-density lipoprotein
LSP	Laboratory Standardization Panel
NCEP	National Cholesterol Education Program
NHANES III	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NRS/CHOL	National Reference System for Cholesterol
VA	Veterans Affairs
VLDL	Very-low-density lipoprotein

Chapter 1

Introduction

The National Institutes of Health (NIH) emphasizes lowering cholesterol as an important aspect of preventing coronary heart disease. In 1985, NIH's National Heart, Lung, and Blood Institute (NHLBI) initiated the National Cholesterol Education Program (NCEP), which has undertaken a major effort to encourage individuals to measure, track, and reduce their cholesterol levels (notably total and low-density lipoprotein (LDL) cholestrol) with the objective of reducing mortality and morbidity from coronary heart disease. The focus on cholesterol reduction has come at a time when increased emphasis has also been given to modifying other risk factors associated with heart disease such as cigarette smoking and hypertension.

One aspect of the efforts to broaden awareness of cholesterol as a risk factor has been to encourage individuals to "know your cholesterol number." This advice has been heeded by the public. According to data compiled by the Centers for Disease Control and Prevention (CDC) from 47 states and the District of Columbia, the percentage of adults who reported having had their total cholesterol checked in the past 5 years ranged from 56 percent in New Mexico to 71 percent in Connecticut (median across the states sampled: 64 percent). The percentage of persons who had been told their cholesterol is high by a health professional ranged from 14 percent in New Mexico to 21 percent in Michigan (median across the states sampled: 17 percent).[1]

For a widespread cholesterol-lowering campaign to be credible, however, test results must be accurate across the diverse devices and settings in which cholesterol is measured. This is because the guidelines for treating elevated cholesterol are predicated on test results that place an individual into different risk categories. In this report, we discuss what is known about the accuracy of cholesterol testing, including how it is measured, factors that hinder accurate measurements, and efforts to improve the accuracy of cholesterol tests.

Background

Coronary heart disease is one of the leading causes of death for both men and women in the United States, accounting for 478,530 deaths in 1991, according to the American Heart Association (AHA). Of these deaths, 52 percent were men and 48 percent were women. Approximately 6.3 million people alive today in the United States have a history of heart attack, chest pain, or both; of this group, 44 percent are 60 years of age and older, 25 percent are 40 to 59 years old, and 31 percent are younger than 40.

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[1] These figures were collected in 1991 through CDC's Behavioral Risk Factor State Survey.

Further, 1.5 million Americans are expected to suffer a heart attack in 1994. The death rate from heart attack in the United States, however, declined 32 percent between 1981 and 1991.[2] Reasons cited as contributing to this decline include improved medical care of patients and preventive measures in the population.[3]

AHA estimates that total costs associated with coronary heart disease are $56.3 billion per year. Of this figure, $37.2 billion is spent on hospital and nursing home services, $8.7 billion on physicians and nurses services, and $2.4 billion on drugs. Lost output associated with heart disease is valued at $8 billion.[4]

Because of the large sums being spent on treatment, to say nothing of the attendant psychological and social costs, prevention has been emphasized. NHLBI has established several education programs, such as NCEP, to inform the public about different risk factors associated with coronary heart disease and to provide guidelines for reducing risks that are modifiabl Other programs include the National High Blood Pressure Education Program, which began in 1972; the Smoking Education Program (1985); and the Obesity Education Initiative (1991).

NCEP Guidelines

A consensus development conference of scientific experts brought together by NIH in 1984 concluded that the risk of coronary heart disease is positively related to increased levels of serum cholesterol and that lowering elevated cholesterol levels can reduce coronary heart disease risk for individuals. The conference experts based their conclusions on the accumulated evidence from a large body of epidemiological, animal, metabolic, and clinical studies. Of major importance was the results of the Lipid Research Clinics Coronary Primary Prevention Trial, a large randomized study completed in 1984 that provided evidence that treatment to lower high cholesterol levels in patients can reduce the risk of coronary heart disease.[5] The conference experts further recommended plans for establishing the National Cholesterol Education Program, whic began in 1985.

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[2] American Heart Association, Heart and Stroke Facts: 1994 Statistical Supplement (Dallas, Texas: 1993), p. 10.

[3] Committee on Diet and Health, National Research Council, Diet and Health: Implications for Reducing Chronic Disease Risk (Washington, D.C.: 1989).

[4] American Heart Association, p. 22.

[5] Funded by NIH, the Lipid Research Clinics trial studied 3,806 middle-aged men with high serum cholesterol levels (mean baseline total cholesterol of 280 mg/dL) and no known symptoms of coronary heart disease. After 7.4 years of follow-up, the incidence of coronary heart disease events (myocardial infarction and sudden cardiac death) was reported to be 7 percent for those in the drug treatment group (cholestyramine) compared to 8.6 percent for those in the placebo group, a 19-percent relative risk reduction (significant at $p < .05$).

NCEP has convened several expert panels and issued a series of guideline reports, and educational materials on the management and control of cholesterol for health care professionals and the general public. The program emphasizes two parallel approaches: (1) a clinical approach tha attempts to identify and treat individuals who are at high risk and (2) a broader population approach that aims to reduce cholesterol levels for th entire population.

Clinical guidelines for reducing elevated cholesterol levels in adults over 20 years of age were first issued by the Adult Treatment Panel in 1987 an were subsequently updated in a second expert panel report in 1993. Thes guidelines cover the classification of cholesterol, patient evaluation, and dietary and drug treatments In 1990, NCEP outlined population strategies t lower total and LDL cholesterol by encouraging all Americans to be aware that elevated cholesterol is a potential risk factor for coronary heart disease, have their cholesterol measured at regular intervals, and modify their diet. NCEP published another report in 1991 that addressed cholesterol issues in children and adolescents. It emphasized strategies fo encouraging the nation's youths to reduce their intake of saturated fat an cholesterol as well as identifying and treating those whose high serum cholesterol levels put them at increased risk for heart disease as adults. The recommendations made in NCEP reports are disseminated and implemented through 40 agencies, such as AHA, that conduct health education and information activities.

Adult Treatment Guidelines

The current NCEP adult treatment guidelines emphasize classification and treatment decisions based on a person's risk status, which is defined not only by serum cholesterol levels (including total cholesterol and its low-density lipoprotein (LDL) and high-density lipoprotein (HDL) components) but also by what other coronary risk factors are present. Those with symptoms of coronary heart disease or with at least two other coronary heart disease risk factors are considered candidates for more intensive treatment.

Positive risk factors are

- Hypertension (≥140/90 mm Hg, or on antihypertensive medication)
- Current cigarette smoking

- Diabetes
- Family history of myocardial infarction or sudden death before age 55 in father or male sibling, before age 65 in mother or female sibling
- Age: male ≥45 years of age or female ≥55 years of age or postmenopausal and not on estrogen replacement therapy
- Low HDL cholesterol (<35 mg/dL)

A negative risk factor is

- HDL cholesterol ≥60 mg/dL.[6]

The guidelines recommend that all adults have their total cholesterol measured at least once every 5 years and that HDL cholesterol be measured at the same time. As shown in figure 1.1, adults without evidence of existing coronary heart disease are classified initially into three levels based on total cholesterol levels—desirable (below (<) 200 mg/dL), borderline high (200-239 mg/dL), and high (equal to or above (≥) 240 mg/dL). An HDL cholesterol level of less than 35 mg/dL is considered low and a contributing risk factor for coronary heart disease. The cutpoints for total cholesterol are based largely on epidemiological data that have shown that the risk of heart disease increases as cholesterol levels rise. For example, in 361,000 men screened for the Multiple Risk Factor Intervention Trial, those at or above the 90th percentile of total cholesterol, about 263 mg/dL, had a four times greater risk of death from coronary heart disease than those in the bottom 20 percent (< 182 mg/dL).[7]

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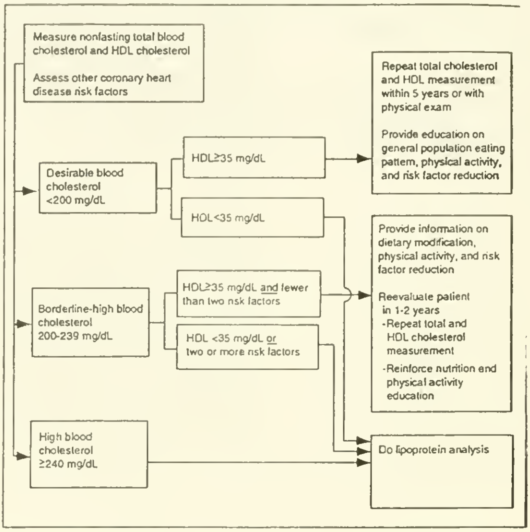
[6] An HDL cholesterol level greater than or equal to 60 mg/dL is considered to be a negative risk factor because at this level it appears to have a protective effect against coronary heart disease. Our source for positive and negative risk factors is "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," National Cholesterol Education Program, Bethesda, Maryland, 1993.

[7] M. J. Martin et al., "Serum Cholesterol, Blood Pressure, and Mortality: Implications from a Cohort of 361,662 Men," Lancet, 2 (1986), 933-36.

Figure 1.1: Primary Prevention in Adults Without Evidence of Coronary Heart Disease: Total and HDL Cholesterol

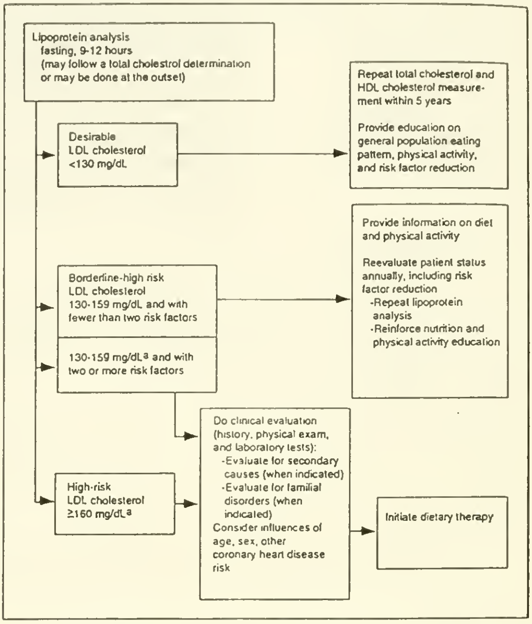

Measure nonfasting total blood cholesterol and HDL cholesterol
Assess other coronary heart disease risk factors
Desirable blood cholesterol <200 mg/dL
HDL≥35 mg/dL
HDL<35 mg/dL
Repeat total cholesterol and HDL measurement within 5 years or with physical exam
Provide education on general population eating pattern, physical activity, and risk factor reduction
Borderline-high blood cholesterol 200-239 mg/dL
HDL≥35 mg/dL and fewer than two risk factors
HDL <35 mg/dL or two or more risk factors
Provide information on dietary modification, physical activity, and risk factor reduction
Reevaluate patient in 1-2 years
-Repeat total and HDL cholesterol measurement
-Reinforce nutrition and physical activity education
High blood cholesterol ≥240 mg/dL
Do lipoprotein analysis

Source: "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," National Cholesterol Education Program, Bethesda, Maryland, 1993.

As indicated in figure 1.1, individuals are recommended for a followup lipoprotein analysis depending on an assessment of their total cholesterol and HDL cholesterol levels in conjunction with the presence or absence of other coronary heart disease risk factors. Thus, those who would be candidates for a subsequent lipoprotein analysis include individuals with (1) high total cholesterol (≥240 mg/dL), (2) borderline-high cholesterol (200-239 mg/dL) and low HDL cholesterol (<35 mg/dL), or
(3) borderline-high cholesterol (200-239 mg/dL), higher HDL cholesterol (>35 mg/dL), and two or more risk factors.

Lipoprotein analysis includes measurement of fasting levels of total cholesterol, HDL cholesterol, and triglycerides and the calculation of LDL cholesterol, which is derived by a mathematical formula. The subsequent classification of adults based on LDL cholesterol levels is shown in figure 1.2. NCEP also classifies LDL cholesterol into three levels—desirable (<130 mg/dL), borderline-high risk (130-159 mg/dL), and high risk (≥160 mg/dL) Decisions for beginning diet or drug treatment are then based on these levels in combination with other risk factors (see table 1.1). Thus, candidates for diet therapy without known symptoms of coronary heart disease include those with high LDL cholesterol (≥160 mg/dL) or those wi borderline-high LDL cholesterol (130-159 mg/dL) plus two or more risk factors.

Figure 1.2: Primary Prevention in Adults Without Evidence of Coronary Heart Disease: LDL Cholesterol


Lipoprotein analysis
fasting, 9-12 hours
(may follow a total cholestrol determination or may be done at the outset)
Desirable
LDL cholesterol
<130 mg/dL
Repeat total cholesterol and HDL cholesterol measurement within 5 years
Provide education on general population eating pattern, physical activity, and risk factor reduction
Borderline-high risk
LDL cholesterol
130-159 mg/dL and with fewer than two risk factors
Provide information on diet and physical activity
Reevaluate patient status annually, including risk factor reduction
-Repeat lipoprotein analysis
-Reinforce nutrition and physical activity education
130-159 mg/dLa and with two or more risk factors
Do clinical evaluation (history, physical exam, and laboratory tests):
-Evaluate for secondary causes (when indicated)
-Evaluate for familial disorders (when indicated)
Consider influences of age, sex, other coronary heart disease risk
High-risk
LDL cholesterol
≥160 mg/dLa
Initiate dietary therapy

[a] On the basis of the average of two determinations. If the first two LDL cholesterol tests differ by more than 30 mg/dL, a third test should be obtained within 1 to 8 weeks, and the average value of the three tests should be used.

Source: "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," National Cholesterol Education Program, Bethesda, Maryland, 1993.

Table 1.1: Treatment Recommendations Based on LDL Cholesterol[a]

Treatment	With or without coronary heart disease	LDL level to begin treatment	LDL goal of treatment
Dietary	Without and fewer than two risk factors	≥160	<160
	Without and two or more risk factors	≤130	<130
	With	>100	≤100
Drug	Without and fewer than two risk factors	≥190[b]	<160
	Without and two or more risk factors	≥160	<130
	With	≥130[c]	<100

[a] All values are in mg/dL.

[b] In men under 35 years and premenopausal women with LDL cholesterol levels 190-219 mg/dL, it is recommended that drug therapy be delayed except in high-risk patients like those with diabetes.

[c] In coronary heart disease patients with LDL cholesterol levels 100-129 mg/dL, it is recommended that the physician exercise clinical judgment in deciding whether to initiate drug treatment.

Source: "Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," National Cholesterol Education Program, Bethesda, Maryland, 1993.

NCEP recommends diet therapy as a first line of treatment for most patients except those at particularly high risk who may warrant drug intervention immediately, such as individuals with existing coronary heart disease. NCEP's recommended step I and step II diets are designed to reduce consumption of saturated fat and cholesterol and to promote weight loss in overweight patients.[8] If diet therapy is ineffective at lowering LDL cholesterol levels, then drug treatment is advised. NCEP has developed a series of guidelines for administering different types of drugs that are available to lower cholesterol. It should be noted that initiating drug treatment commits patients to long-term therapy, which may be for the rest of their lives.

Some perspective on what these treatment categories and recommendations mean for Americans can be seen in recently collected, nationally representative data from the first phase of the National Health and Nutrition Examination Survey (NHANES III).[9] These data indicate that the average total serum cholesterol level is 205 mg/dL for men 20 years old and older and 207 mg/dL for women 20 years old and older. As shown in figure 1.3, women tend to have lower total cholesterol levels compared to men up until the ages of 45 to 54, at which time it increases to levels above those of men. This difference may be attributed, in part, to menopause, which influences women's lipid and hormonal levels. Whether this increases women's coronary heart disease risk is not clear, according to some research. Overall, women appear to have higher HDL cholesterol levels then men do, which may also account for part of this difference.[10]

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[8] The step I diet includes the following conditions: saturated fat consumption of 8-10 percent of total calories, 30 percent or less of calories from total fat, and cholesterol less than 300 mg/day; the more stringent step II diet lowers saturated fat consumption to less than 7 percent of total calories and cholesterol to less than 200 mg/day.

[9] C. L. Johnson et al., "Declining Serum Total Cholesterol Levels Among U.S. Adults: The National Health and Nutrition Examination Surveys," Journal of the American Medical Association, 269 (1993), 3002-8.

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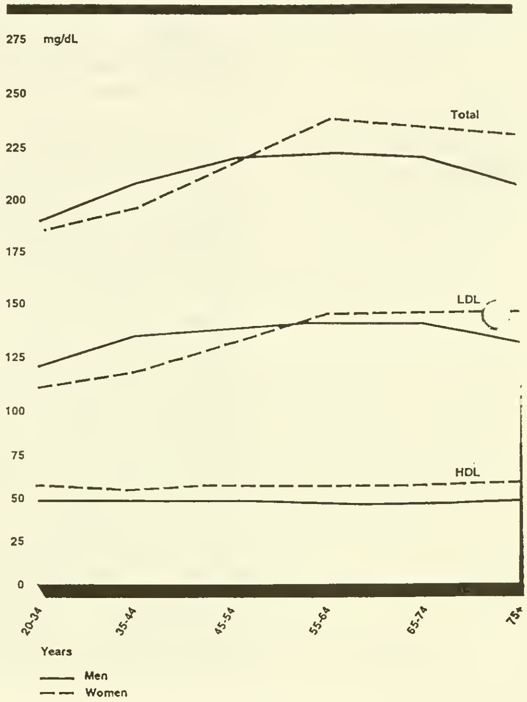
[10] Differences in HDL levels by gender were consistent across racial groups. In non-Hispanic blacks, men's HDL levels averaged 53 mg/dL, women's 58 mg/dL. Mexican-American men had an average HDL of 47 mg/dL and women 53 mg/dL. Non-Hispanic white men had the lowest average HDL levels (46 mg/dL) while women in this group averaged 56 mg/dL.

Figure 1.3: Total, LDL, and HDL Serum Cholesterol Levels for U.S. Adults 20 Years Old and Older



While trend data indicate that cholesterol levels have declined since the early 1960's, 52 million U.S. adults, or 29 percent, have an LDL cholesterol level that is classified as borderline-high or high according to the NCEP guidelines and that, when combined with other risk factors, makes them candidates for dietary therapy.[11] Of the 52 million adults mentioned abov about 12.7 million have cholesterol levels sufficiently elevated that they might be candidates for drug therapy (about one third of this group woul be patients with coronary heart disease).

Cholesterol Measurement Recommendations

NCEP's Laboratory Standardization Panel (LSP) has issued two reports on cholesterol measurement. The first report, issued in 1988, focused attention on the importance of accurate measurements. In the report's introduction, the panel stated: "the current state of reliability of blood cholesterol measurements made in the United States suggests that considerable inaccuracy in cholesterol testing exists."[12] That report, alon with press articles critical of cholesterol testing in 1987, drew attention t the need for more consistent and replicable results.

In addition to outlining the state of the art in cholesterol testing, the NCEP/LSP reports describe factors that can affect test accuracy and reliability: analytical problems (laboratory analyzer inaccuracy and imprecision) and preanalytical factors (biological variation, disease, conditions under which a sample is taken). The second report published i 1990 also contains a number of recommendations to improve laboratory testing systems. These include using only analytical systems whose standardization process is linked to the National Reference System for Cholesterol (NRS/CHOL, discussed in chapter 3), participating in external surveillance programs (proficiency testing), comparing results with other laboratories, and using quality controls to monitor analytical performanc

Recognizing the problem of measurement variability in cholesterol testin the Adult Treatment and Laboratory Standardization Panels recommende that total and LDL cholesterol be measured on two separate occasions and averaged together. If the cholesterol results differ by 30 mg/dL or more, then a third test should be conducted and the three tests averaged togeth to assess an individual's cholesterol level.

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[11] According to the government's Interagency Board for Nutrition Monitoring and Related Research, doctor-recommended diets to lower cholesterol rose 6 percent between 1983 and 1990. In 1990, 15 percent of the population followed self-prescribed diets to lower cholesterol and slightly less than 10 percent were on doctor-recommended diets. See Nutrition Monitoring in the United States: Selected Findings from the National Nutrition Monitoring and Related Research Program (Hyattsville, Md.: 1993), p. 63.

[12] Laboratory Standardization Panel, National Cholesterol Education Program, Current Status of Cholesterol Measurement in Clinical Laboratories in the United States (Bethesda, Md.: 1988), p. 1.

NCEP/LSP established the goal that a single serum total cholesterol measurement should be accurate within ±8.9 percent. This goal of ±8.9 percent was effective in 1992, replacing the interim goal of ±14.2 percent that had been established in 1988.[13] NCEP has not previously issued goals for HDL and LDL cholesterol measurement; however, an expert panel convened by NCEP has recently developed such goals and they are expected to be published shortly.

The Clinical Laboratory Improvement Amendments of 1988 (Public Law 100-578) also mandated that the Secretary of Health and Human Services (HHS) establish performance standards such as quality control, quality assurance, and personnel regulations. HCFA testing requirements for total cholesterol, authored by CDC, stipulate a ±10 percent criterion for acceptable performance for proficiency testing purposes. HCFA testing requirements for HDL cholesterol for acceptable performance on proficiency testing specimens is ±30 percent of the established target value.

Although the NCEP guidelines advocate multiple measurements, there has been concern by some researchers that, in practice, physicians may not take measurement variability into account when making treatment decisions about cholesterol. Given that the NCEP classification levels for cholesterol are relatively narrow and that the average cholesterol levels for the U.S. population are in the borderline-high category at about 205 mg/dL, there is potential that patients can be misclassified. That is, measurement errors can lead to individuals with "true" levels below the high cutpoint of 240 mg/dL for total cholesterol or 160 mg/dL for LDL cholesterol being put on treatment (termed a false positive) or conversely those with "true" levels above the cutpoints not being treated (a false negative).

Objectives, Scope, and Methodology

In discussions with the requester, we agreed to focus our review of cholesterol measurement on the following evaluation questions:[14]

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[13] The total error goal is ≤3 percent bias and ≤3 percent imprecision, at the 0.05 level of significance, 2-tailed test. This means that if an individual's true total cholesterol were 200 mg/dL, and the same specimen were tested 100 times, 95 of these tests should fall between 182.2 and 217.8 mg/dL. Clinical chemists use the measurement term "precision" differently from social scientists and evaluators [illegible]s used to describe what social scientists term "reliability"—that is, whether a test or measure giv[illegible] same result on repeated trials.

[14] In a subsequent study, we will report on issues pertaining to the clinical trials evidence that supports the NCEP guidelines.

1. How is cholesterol measured? (See chapter 2.)

2. What is known about the accuracy and precision of cholesterol measurement techniques? (See chapter 3.)

3. What factors influence cholesterol levels? (See chapter 4.)

4. What is the potential effect of uncertain measurement? (See chapter 5.)

To answer these questions, we identified and reviewed relevant scientific literature published mainly since 1988 and synthesized data across studies to address these questions. We selected this period because it covered the time since the first NCEP cholesterol measurement goals were issued, permitting a benchmark by which later testing could be judged. We conducted our bibliographic search using on-line data bases of medical literature. Other sources included articles recommended by experts in the field and the bibliographies of articles published in medical and related research journals. We identified and reviewed approximately 125 books and articles relevant to cholesterol measurement in this manner.

We supplemented our review of the medical literature with interviews with a range of individuals who have expertise in the field. These included government agency officials involved with cholesterol measurement and testing issues at CDC, the Food and Drug Administration (FDA), HCFA, NIH, and the National Institute of Standards and Technology (NIST). We also interviewed manufacturers of analyzers in private industry, university researchers, and representatives of organizations that conduct proficiency testing for laboratories. In order to have a better understanding of the testing process, we visited a major hospital laboratory facility to discuss quality control issues and challenges facing practitioners. We also visited a major manufacturer of analyzers to learn more about the production process (quality control procedures, analyzer calibration, potential sources of inaccuracy) as well as industry concerns about the accuracy and precision of cholesterol testing. We did not, however, independently evaluate laboratory performance in any of the different settings where cholesterol tests are conducted across the country.

Chapter 2

Cholesterol Measurement: Methods, Settings, and Analyzers

In this chapter, we answer the first evaluation question: How is cholesterc measured? The discussion begins with an overview of cholesterol's role in the body and analyzes how total cholesterol, HDL, LDL, apolipoproteins, an triglycerides are measured, focusing on laboratory techniques. We also describe the range of settings where cholesterol testing is done and reviev the type of analyzers for sale in the U.S. market.

Cholesterol measurement focuses mainly on determining levels of total, HDL, and LDL cholesterol. Triglyceride levels are also included in lipid profiles. Cholesterol is commonly tested in a variety of settings ranging from large health fairs to more specialized clinical laboratories. No national data are available on the number of laboratories that conduct cholesterol tests, the number of cholesterol testing devices in use in laboratories, or the number of such tests that are done each year. The universe of U.S. laboratories that conduct different types of medical tests is large, however, with some 154,403 having registered with HCFA by October 1993. While HCFA data indicate that physicians' offices predominate in the testing arena, the distribution of cholesterol tests no ascertainable from these data. Test results may be less accurate from sucl settings because of the type of devices used and less staff expertise in conducting tests.

In addition to the broad range of settings where measurements are conducted, a large number of analyzers on the market measure cholestero (45 manufacturers make 166 test systems that measure total cholesterol). Because some of these analyzers are used with different chemical formulations to conduct cholesterol tests, standardizing measurements is a complex task (a topic taken up in chapter 3). A related measurement issue is the use of enzymatic materials in cholesterol analyzers. While enzymatic materials have permitted improvements in ease of use, they are difficult to characterize chemically because they may deteriorate or vary with time, introducing potential measurement inaccuracy.

Cholesterol's Role in the Body

While considerable attention has been given to the negative consequences of elevated total and LDL cholesterol levels, cholesterol is essential to body processes, affecting the production of steroid hormones and bile acids as well as being a structural component of cellular membranes.Cholesterol is a fat-like substance (lipid) manufactured by the body and is also ingested directly through foods such as eggs, which contain cholesterol. In addition, certain saturated fats raise the blood cholesterol level more n any other nutrient component in the diet. If you eat a "standard" American diet, two thirds of the cholesterol in your body is manufactured by your cells—the remainder is derived from your diet. Thus, an elevated cholesterol level may be the result of a diet heavy in saturated fat and cholesterol; it is also possible that the liver is manufacturing high levels of cholesterol and triglyceride or that cholesterol is being removed too slowly from the body.

Cholesterol is transported in blood plasma through lipoproteins. The three major classes of lipoproteins include LDL (containing 60 to 70 percent of the total serum cholesterol), HDL (containing 20 to 30 percent of the total serum cholesterol), and VLDL (very low density lipoproteins, which are precursors of LDL and contain 10 to 15 percent of the total serum cholesterol). Triglycerides are also an important lipid in the blood and are usually measured in conjunction with cholesterol values. More recently, increased scientific attention has been given to the apolipoprotein "families," the subcomponents that make up these types of cholesterol, because they may be better predictors of certain risks associated with coronary heart disease such as degenerative changes in arterial walls. At present, however, research on this topic continues to be developed and tests for measuring apolipoproteins cannot be done in most laboratories.

Total Cholesterol Measurement

Of the different cholesterol types, total cholesterol is the best understood and documented, in large part because of work done at NIST and CDC to standardize measurement techniques (see chapter 3). In general laboratory practice, total cholesterol measurement is commonly accomplished by several different enzymatic methods using a variety of reagent materials.[1] The various procedures used make standardization of technique across different reagents and instrument configurations difficult.

HDL Cholesterol Measurement

HDL cholesterol, sometimes referred to as the "good" cholesterol, has become recognized as an important coronary heart disease risk factor. HDL is the smallest in size of the lipoproteins and its major subcomponents are apo AI, or apolipoproteins AI, and apo AII. Because a validated reference method has not been developed for HDL measurement, a patient specimen comparison with CDC's procedure is considered the best means to assess accuracy. HDL cholesterol is difficult to measure accurately, however, and current criteria under the Clinical Laboratory Improvement Amendments of 1988 for acceptable laboratory performance are that a sample must be ±30 percent of a test target value, a relatively broad range even with lower HDL values. CDC officials we interviewed pointed out that considerable scientific work remains before HDL measurement accuracy is as well understood as total cholesterol currently is. This would include developing accurate reference materials that could be used to evaluate how well analyzers are measuring HDL cholesterol.

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[1] For discussion of different total cholesterol measurement methods, see J. D. Artiss et al., "Measurement of Cholesterol Concentration," in Methods for Clinical Laboratory Measurement of Lipid and Lipoprotein Risk Factors, N. Rifai and G. R. Warnick (eds.) (Washington, D.C.: AACC Press, 1991), pp. 33-50.

LDL Cholesterol Measurement

Low-density lipoprotein cholesterol, sometimes referred to as the "bad" cholesterol, is considered to be the principal fraction that causes plaque to build up on arterial walls. No error standards for LDL cholesterol measurement have been established under the Clinical Laboratory Improvement Amendments of 1988 or NCEP, although NCEP expects to issue such standards shortly. Direct measurement of LDL cholesterol can be accomplished through ultracentrifugation methods; however, such methods are expensive and time consuming to conduct and therefore not generally available in most cholesterol test settings.[2]

In practice, LDL cholesterol is calculated from other laboratory measurements using the Friedewald formula: LDL = total cholesterol – HDL – (triglycerides/5). Among the several limitations to the Friedewald formula is that a patient should be fasting when the specimen is taken. The formula cannot be used for individuals with extremely high triglyceride levels (400 mg/dL and above) and several rare lipid conditions. The most crucial constraint related to the Friedewald formula is that because it relies heavily on the accuracy and precision of total cholesterol, HDL, and total triglycerides, potential measurement error is compounded.

Triglycerides

Triglyceride levels are usually measured along with lipoprotein levels because they are considered an important health indicator for certain diseases, including coronary heart disease in some patients. Triglycerides are also important to measure because they are used to calculate LDL cholesterol with the Friedewald equation. Enzymatic methods are used to analyze triglyceride levels, although the calibration of such methods is not linked to a validated definitive or reference method. As with HDL and LDL cholesterol, the CDC method (in this case, a chemical chromatropic acid method) is considered the best means for comparing accuracy. Current criteria under the 1988 amendments for acceptable laboratory performance are that a sample must be ±25 percent of a proficiency test target value.

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[2] There has been one recent advance in LDL measurement. A private company, Genzyme, has introduced a direct LDL cholesterol measure that permits testing to be done in a nonfasting state. This method could eliminate the need for multiple tests as well as provide added patient convenience.

Apolipoprotein Measurement

As analytical capabilities have increased, attention has also turned to the apolipoproteins, which make up HDL and LDL cholesterol. This interest is linked to finding other relevant markers for coronary heart disease risk. For example, recent research has focused on apolipoprotein B-100 (apo B), which is an integral component of four major lipoproteins—LDL, VLDL, intermediate density lipoprotein, and lipoprotein(a)—and apo AI, the major protein component of HDL. At present, several assay methods are available to measure different apolipoprotein components; however, these methods have not yet been standardized. Another practical difficulty in using these apolipoproteins is that a comprehensive, statistically sound study has not yet been undertaken that can be used as a comparative reference base.

The Use of Ratios to Determine Coronary Heart Disease Risk

One issue addressed in the medical literature concerns combining cholesterol levels to determine a ratio that is used to evaluate a patient's risk of developing coronary heart disease—for example, a total cholesterol or LDL to HDL ratio. In some instances, individuals are advised to achieve a specific ratio as an indicator of an acceptable cholesterol level. Such ratios have been useful estimators of coronary heart disease risk in some population studies; however, NCEP emphasizes that HDL and LDL cholesterol levels are independent risk factors with different determinants and should not be combined for clinical decisionmaking.

Test Settings

Widespread awareness of elevated total cholesterol levels as a potential coronary heart disease risk factor has led to patient testing in a variety of settings. These range from traditional clinical settings (hospitals, physician office laboratories) to mass screenings (such as health fairs). No national data are available on the number of laboratories that conduct cholesterol tests, the number of cholesterol testing devices in use in laboratories, or the number of such tests that are done each year.

The Clinical Laboratory Improvement Amendments of 1988 changed federal regulation of laboratories and expanded federal oversight to virtually all testing laboratories in the nation. The amendments required all laboratories to register with HCFA and established testing and quality control standards, including provisions for conducting inspections to ensure that laboratories are maintaining proper controls and records. In implementing the act, the Secretary of HHS established three categories o laboratory tests: (1) simple tests, (2) tests of moderate complexity, and (3) tests of high complexity. Waivers are given to laboratories that cond only simple tests such as dipstick or tablet reagent urinalysis. Cholestero tests are in the moderate complexity group, meaning that laboratories th perform such tests should comply with regulations under the amendmen for personnel standards, quality control, and proficiency testing (these tests evaluate accuracy and precision using quality control materials).

As of October 1993, 154,403 laboratory facilities in the United States had registered with HCFA. HCFA officials estimate that there may be as many as 50,000 additional laboratories that should have registered with HCFA but have not, making it impossible to determine the universe of such facilitie Table 2.1 categorizes laboratories that had registered with HCFA. Of the registered laboratories, the majority, 90,673 (58.7 percent), are located in physicians' offices.

Table 2.1: Types of Laboratories Registered With HCFA[a]

Type of laboratory	Number	Percent
Physician's office	90,673	58.7%
Nursing facility	11,872	7.7
Hospital	8,922	5.8
Community clinic	7,063	4.6
Independent	6,302	4.1
Home health agency	5,083	3.3
Other practitioner	2,714	1.8
Ancillary testing site in health care facility	2,115	1.4
End-stage renal disease dialysis facility	1,614	1.0
Industrial	1,154	0.7
Ambulatory surgical center	1,000	0.6
Health maintenance organization	979	0.6
School or student health service	834	0.5
Mobile unit	603	0.4
Intensive care facility	516	0.3
Health fair	489	0.3
Pharmacy	304	0.2
Hospice	301	0.2
Blood bank	284	0.2
Tissue bank or repository	77	0
Comprehensive outpatient rehabilitation facility	66	0
Insurance	43	0
Other	10,380	6.7
Unknown	1,015	0.7
Total	154,403	100.0%

[a] That is, laboratories regulated under Public Law 100-578. These classifications are based on how laboratories classified themselves when surveyed by HCFA.

Source: Health Care Financing Administration, Baltimore, Maryland, October 1993.

Oversight of the laboratories listed in table 2.1 varies, depending on the level of tests performed and several factors. A large number, 67,000, conduct only tests that are not medically complex and are therefore exempt from regulation; 6,500 are accredited by a state agency; 24,000 are accredited by nongovernment proficiency testing groups; 16,000 conduct microscopic tests under HCFA oversight. HCFA coordinates biannual, on-site inspections by state agencies and HCFA regional office laboratory consultants for the remaining 41,000 laboratories.

HCFA expects to have 180 state agency surveyors nationwide who will w
under 10 different HCFA regional offices.[3] On-site inspections will consist
examining a sample of laboratory tests based on volume, specialties, clients, and the number of shifts over which equipment is used. In their inspections, surveyors will look at the following five areas: patient test management and organization, results of proficiency tests, personnel qualifications, quality assurance procedures, and use of daily quality controls.

HCFA staff began laboratory inspections under the 1988 amendments in September 1992 and they hope to have the first cycle of visits and certifications completed by March 1995. The initial emphasis of inspections has been to educate and inform laboratory personnel about pertinent regulations. HCFA staff responsible for overseeing laboratory inspections stated that of the 6,200 survey visits that had been made by August 1993, 500 laboratories were found to have major deficiencies (th
nature of these problems was not specified).

HCFA survey and certification officials and NCEP have expressed concern that cholesterol testing in physicians' offices or screening settings may differ from that done in clinical and research settings. For instance, clinical laboratories or hospitals may be more likely to have well-established quality control programs and large analyzers while physicians' offices or health fairs may be limited to less reliable desk-top analyzers and less expertise in conducting tests and maintaining analyze
(see the discussion of analyzer types in chapter 3). HCFA staff stated that physicians' offices often send specimens for HDL and LDL tests to larger laboratories, which have the capability to do these tests.

While enforcement under the 1988 amendments is relatively new, each o
the groups most affected—HCFA, laboratory personnel, and proficiency testing service providers—views it differently. HCFA officials noted from their experience overseeing laboratories that the traditionally unregulate
segment of the medical testing market, physicians' office laboratories, se
the regulations as a burden and an added cost. In contrast, laboratories that have maintained a high-quality testing program believe the regulatio
represent minimum standards for running a quality testing program. Proficiency testing service providers have had to confront problems with the quality control materials they use to assess and transfer accuracy

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[3] When the Clinical Laboratory Improvement Amendments of 1988 was enacted, it was expec at
the various agency regulatory activities would be fully implemented by 1991. However, the development of regulations was complex and time consuming, thus delaying the program start-up
1992.

among laboratories, attempting to balance the limits of these materials with how they are used to judge laboratory performance. All agree, however, that meeting the standards adds to the cost of testing.

There are also several types of nonmedical settings in which testing is routinely undertaken: health fairs, shopping malls, and the workplace. In some cases, only a small amount of blood taken from the finger (capillary source) is used to conduct such a cholesterol analysis. These testing environments are subject to a variety of potential problems, however: poorly trained personnel taking samples, inappropriate patient preparation, incorrect specimen collection, or improperly calibrated analyzers. There is also concern that in nonmedical settings individuals may be given test results without proper interpretation. An additional concern is that those who need to be referred for further medical consultation or a more detailed cholesterol profile may not receive that advice.

Cholesterol Analyzers

FDA reviews and clears diagnostic devices, including those that measure cholesterol. Following section 510(k) of the Food, Drug, and Cosmetic Act of 1976, device manufacturers must notify FDA that they intend to market a device. FDA then determines whether the device is accurate, safe, effective, and substantially equivalent to a legally marketed "predicate" device—that is, one that was on the market when this law was passed. If the agency determines that a device does not meet 510(k) guidelines and deems it not substantially equivalent, then it must be reviewed as a new product. According to agency officials, FDA's review of cholesterol measurement devices takes into consideration information provided by manufacturers on intended use, test type and methodologies, performance characteristics (derived from actual assays), analytical performance for 40 normal and 40 abnormal specimens across the range of cholesterol levels, and label wording (intended use statement and conditions).

FDA officials indicated that the agency requests that cholesterol device manufacturers compare their analyzers to the accuracy and precision methods of the National Reference Method Laboratory Network for total cholesterol measurement (see chapter 3). However, FDA does not formally require that analyzers be "traceable" to this method because there are devices on the market that have not established "traceability" to the reference method (traceability refers to the ability of a device to closely duplicate the accuracy attained by the reference method).

CDC has compiled a list of total and HDL cholesterol analyzers currently in use. As of April 1994, there were 166 test systems (made by 45 different manufacturers) available to measure total cholesterol. For HDL cholesterc 143 test systems, made by 41 manufacturers, have been identified. (Some manufacturers have as many as 11 "systems" that use the same technology.)

FDA-cleared cholesterol analyzers encompass three types of devices: large stationary analyzers used in clinical laboratories, desk-top analyzers, and home test kit analyzers. Desk-top analyzers can be used in a variety of settings (medical and nonmedical) to provide relatively quick cholesterol test results, whereas large analyzers are capable of performing multiple tests on many analyses for hundreds of specimens a day. The latter are usually found in large independent laboratories, hospital laboratories, and the offices of major testing organizations that serve the medical community.

The third type is a home test kit, designed for sale directly to consumers. Currently, one device, the AccuMeter (manufactured by ChemTrak) is being marketed in the United States. The approval of this device has been somewhat controversial in the clinical chemistry field because of concern about the reliability of its measurements. Apart from possible technical problems is the related issue of whether a person may incorrectly interpre his or her cholesterol level after using the device or initiate a self-treatment program without proper medical feedback and monitoring.

Cholesterol analyzers currently on the market primarily use enzymatic methods, high-technology equipment, and computerized data processing systems. Enzymatic methods offer advantages over older chemicals because they are safer and can be used in an automated laboratory environment, both distinct improvements. Nonetheless, enzymatic methods are also considered to be difficult to characterize chemically, thus adding to the uncertainty of tests done with them. FDA draft guidelines for approving cholesterol testing devices note that because enzymatic materials may deteriorate or vary, analyses done with them may be imprecise. A related concern noted by HCFA officials is that each analyzer and reagent combination has its own "method" for measuring cholesterol, making it difficult to assess accuracy using standardized testing materials.

An additional perspective on these devices was provided by a hospital laboratory administrator who observed that the devices used in his laboratory are self-contained "black boxes" that rely heavily on computer technology that must be regularly calibrated as part of a routine quality control process. Unlike the older instruments these have replaced, he noted, these newer devices are easier to use than the older systems. However, their complexity also means that it is hard to determine whether something may be wrong inside the device.

Chapter 3

The Accuracy of Cholesterol Measurements

In this chapter, we answer the second evaluation question: What is know about the accuracy and precision of cholesterol measurement techniques The discussion first focuses on national accuracy goals and efforts to standardize cholesterol measures. This is followed by an analysis of recently published literature that compares test results from different settings.

Standards for cholesterol testing have evolved from the late 1980's, when NCEP first established the goal that total cholesterol measures should be accurate within ±14.2 percent. By 1992, NCEP lowered its total cholesterol measurement goal to ±8.9 percent. HCFA established a similar total cholesterol goal (±10 percent) as well as the goal that HDL cholesterol tes should be within ±30 percent of its correct value, when judged by quality control testing. To date, an LDL cholesterol measurement goal has not bee established, although one is expected soon.

Evaluating the extent to which laboratories across the country are providing medical personnel and patients with accurate total choles[illegible]l test results is difficult. While an accepted national reference system exist and network laboratories can provide traceability to an accuracy standar participation by laboratories has been limited particularly to clinical and research settings. Additional information is collected through proficiency testing surveys that indicate that laboratory precision has improved over time but, again, the number of participating laboratories is small. The lack of information on accuracy in actual laboratory settings makes it impossible to know whether the goals established for total and HDL cholesterol measurement are being met and how well LDL cholesterol is being measured. Because these test results are key to making treatment decisions in NCEP guidelines, such data are arguably important.

Two collaborative research efforts, one by the College of American Pathologists (CAP) and CDC and the other by Veterans Affairs (VA) and CDC, highlight weaknesses of the current system of monitoring cholesterol laboratory tests. The reliance on processed quality control materials for evaluating analyzer accuracy was found to be problematic because of what are termed matrix effects. Processed materials tend to act differentl from fresh serum samples on many instrument reagent systems and produce different test results. The studies found that total cholesterol test done on fresh serum samples in a select group of clinical settings met NCE accuracy standards whereas with processed control materials, there was greater inaccuracy. Finding ways to address matrix problems is imp[illegible]t because processed control materials are key to assessing accuracy across laboratories and serve as the basis for enforcing the Clinical Laboratory Improvement Amendments of 1988.

With regard to desk-top analyzers, there are sufficient concerns about the reported accuracy and precision of total, HDL, and LDL results provided by several devices, even when tested under optimal operating conditions, to warrant further scrutiny of their performance. Consumers should be aware of the potential uncertainty associated with test results produced by these devices, particularly in screening settings. Several studies we reviewed found misclassification rates ranging from 17 to nearly 50 percent.

One new development in the cholesterol testing arena are home test devices, which measure total cholesterol. While these may prove to be useful, questions about their precision and accuracy should not be overlooked—particularly in light of their direct availability to consumers. Broader concerns about how individuals may interpret results and what they might do with that information in terms of failing to seek out appropriate medical consultation and possible treatment are too important to be ignored.

Accuracy, Precision, and NCEP Goals

NCEP's 1990 report, Recommendations for Improving Cholesterol Measurement, established performance goals for assessing the accuracy of individual laboratory testing programs. The report recommended that by 1992 the total error associated with a single serum total cholesterol measurement should be within ±8.9 percent (0.05, 2-tailed test). Total error is defined in terms of two main measurement components: bias and precision. Bias is the extent to which a series of test results deviate from the "true" value, within acceptable limits (≤3 percent according to NCEP), whereas precision refers to the consistency and reliability of repeated results within acceptable limits (≤3 percent according to NCEP). A cholesterol analyzer, for example, could be very precise yet inaccurate because of the poor calibration of an analyzer or the deterioration of the reagents being used. The difference between bias and precision can be illustrated with the following brief example. Suppose that a total cholesterol specimen whose "true" value is 200 mg/dL were tested 10 times on the same analyzer. If the analyzer gave a reading of 220 mg/dL each time it tested the specimen, the analysis would be biased—that is, it would be 10 percent over the "true" value. However, the analysis would be precise in that it consistently gave the same result when testing the specimen—the precision error would be zero.[1]

While test results need to be unbiased and precise, there is the questio how accurate a test need be at particular cholesterol levels. It has been suggested that greater variability may be acceptable at levels well abov below the NCEP cutpoints—for example, at total cholesterol readings o 160 mg/dL or as high as 350 mg/dL. Arguably, accuracy becomes more important near the 240 mg/dL cutpoint than at 350 mg/dL, where there less doubt about a patient's risk category.

The National Reference System for Cholesterol

The National Reference System for Cholesterol (NRS/CHOL) grew out of work undertaken by the National Committee for Clinical Laboratory Standards in 1977 to establish an accuracy base for cholesterol testing. Rather than requiring that all laboratories use the same analyzers and methods to achieve standardization, emphasis is given to having test results traceable to an accepted accuracy standard. NRS/CHOL cons [illegible] o hierarchy of approved methods and materials used to assess cholesterc measurement accuracy. These include basic measurement units and definitive methods (NIST), primary reference materials (NIST), reference methods (CDC), secondary reference materials (NIST and CDC), field methods, and patients' results.[3] These are integrated into an accuracy b that can be transferred through a national laboratory network to devic manufacturers and the broad range of laboratories where cholesterol is measured.

One component of NRS/CHOL involves expertise at NIST, where the defini method for measuring total cholesterol was developed. The definitive method assigns the "true" value to a specimen through a process in whi all potential sources of inaccuracy and interference are evaluated. The definitive method uses an isotope dilution mass spectrometric techniq Because it requires special equipment and costly materials and is time-consuming, the definitive method is not considered transferable t clinical laboratories. This method is also used for the highly specialized purpose of developing and testing standard reference materials that are used by manufacturers and in other settings such as research lipid laboratories.

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[1] Precision is often measured in laboratory tests in terms of the statistical coefficient of variation, which expresses the standard deviation as a percentage of the mean value. It is used to compare precision at different concentration levels. A method's precision varies inversely with the coeffici variation: the lower it is, the more precise the method.

[2] The committee coordinates efforts to promote laboratory standardization among professional, industrial, and government organizations

[3] See R. E. Vanderlinde et al., "The National Reference System for Cholesterol," Clinics in Labora Medicine, 9:1 (1989), 89-104

CDC oversees another piece of NRS/CHOL: it uses what is termed the modified Abell, Levy, Brodie, and Kendall (abbreviated Abell-Kendall) reference method for total cholesterol measurement. When the reference and definitive methods have both been used to test the same samples, the reference method's results have been shown to be about 1.5-percent higher than those of the definitive method.[4]

CDC disseminates the reference method through the National Reference Method Laboratory Network for Cholesterol Standardization. This includes nine laboratories located throughout the United States and four overseas. Because the reference method is expensive and labor intensive, it is not considered practical for use in most clinical laboratories. Consequently, it is used primarily by research laboratories and manufacturers, two settings in which closer traceability to the definitive method is essential.

The network provides a support system that would permit a laboratory o manufacturer to gauge its total cholesterol test accuracy and standardize its measurements.[5] This can be done by splitting samples with a network laboratory and comparing results. Participation in the network is relativel low when one takes into consideration the number of laboratories in the United States. In 1991, for example, 170 laboratories applied for a certificate of traceability and 58 percent passed (if a laboratory fails, it ca reapply for certification). In 1992, 167 laboratories applied for a certificat of traceability and 79 percent passed.

Although participation is low, CDC officials estimate that 95 percent of the types of instrument systems most common in U.S. laboratories have been certified through the reference network as meeting NCEP standards mentioned earlier in this chapter (a list of these analyzers is published in Clinical Chemistry News). CDC representatives caution that the reference laboratories test only an analytical system for potential to meet these standards. Day-to-day consistency in a laboratory requires rigorous quali controls that help ensure that an analyzer will perform as it is capable of performing. In other words, if an analyzer is not maintained properly, it will not provide results that are constantly accurate.[6]

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[4] P. Ellerbe et al., "A Comparison of Results for Cholesterol in Human Serum Obtained by the Reference Method and by the Definitive Method of the National Reference System for Cholesterol," Clinical Chemistry, 36 (1990), 370-75.

[5] Criteria for standardization are a correlation coefficient with the Abell-Kendall 0.975, bias at 200 and 240 mg/dL <3 percent, overall coefficient of variation <3 percent, and average absolute bias <3 percent. Acceptable performance is documented by a dated certificate of traceability that is valid for 6 months.

Another way in which NRS/CHOL attempts to transfer accuracy to laboratories is through "quality control" substances called standard reference materials, which are the link between the definitive and reference methods and manufacturers of analyzers and reagent systems. These include CDC and NIST-produced and certified materials (which are made in stabilized, frozen, or lyophilized, or freeze-dried, forms) that are assigned target values for cholesterol using the reference or definitive methods.

Proficiency Testing Services

Proficiency testing (outside surveillance) services have an increasingly important role in efforts to achieve accuracy and standardization of clinical laboratory tests because they provide the basis for interlaborator comparison of test results and accuracy across analyzers. Proficiency testing programs send quality control materials that participating laboratories analyze and the results are compared with a target value determined by CDC's reference method. These test results are divided into peer groupings (by instrument type), permitting laboratory staff to judge how their results compare with laboratories using the same method as well as the CDC reference method result. CAP and the American Associatio of Bioanalysts are two major groups involved in this work. CAP's Comprehensive Chemistry Survey has 12,000 subscribers that use its service to evaluate several different clinical chemistry tests. This service i not generally used by smaller laboratories. The American Association of Bioanalysts does similar types of proficiency testing.

National trends through 1990 in interlaboratory comparability (that is, the degree to which established test values vary from one laboratory to the next) for total cholesterol are as follows: 1949, 23.7 percent; 1969, 18.5 percent; 1980, 11.1 percent; 1983, 6.4 percent; 1986, 6.2 percent; 1990, 5.5 to 7.2 percent.[7] These data indicate that interlaboratory precision in those clinical laboratories participating in the CAP survey improved considerably from variability of about 24 percent in 1949, to 1983, when it appears to have leveled off at the 6-percent range. These differences between laboratories suggest that method and laboratory-specific biases contributed to overall inconsistency in cholesterol analyses. Another indicator of precision is consistency within individual laboratories. CAP data indicate intralaboratory precision for cholesterol measurements (where participating laboratories analyze the same quality control materials repeatedly over an extended period) improved from 4.1 percent in 1975 to 3.5 percent in 1985.

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[6] Measurement accuracy can also be influenced by how a sample is collected and handled prior to analysis. This includes the use of anticoagulants and preservatives and the temperature at which a specimen is stored (0-4 degrees centigrade is recommended for up to 4 days, −70 degrees centigrade for longer periods).

[7] Figures for 1949 to 1986 were taken from the NCEP/LSP report Current Status of Blood Cholesterol Measurement in Clinical Laboratories in the United States (Bethesda, Md.: 1988), p. 10. The 1990 figures were published in the NCEP report Recommendations for Improving Cholesterol Measurement (Bethesda, Md.: 1990), p. 6.

Matrix Effects

Efforts to achieve standardized, accurate cholesterol measurements through NRS/CHOL and proficiency testing programs have encountered serious problems with the use of quality control (reference) materials. These are termed "matrix" effects and arise when "cholesterol recovered from the control material matrix may not compare with that typically recovered from fresh patient specimens."[8] This is because the matrix surrounding the cholesterol quality control material interferes with the analysis, causing erroneous results (matrix effects do not arise when analyzing fresh blood samples). This is a function of instrument design, reagent composition, method employed, and the material formulation. Because these quality control materials are key to transferring accuracy and quality control in NRS/CHOL and assessing precision in proficiency testing programs, matrix effects present considerable problems. While most attention has focused on matrix effects in quality control materials used to standardize total cholesterol measures, there is also concern that HDL cholesterol control materials may be subject to these effects.

Recent interest in the problems presented by matrix effects is linked to the Clinical Laboratory Improvement Amendments of 1988, which required that proficiency testing be used to evaluate the quality of laboratory results. Matrix problems can make it impossible to assign a target value to quality control material that will apply to all routine testing methods. Industry and academic research efforts are underway to address the measurement problems associated with matrix effects but practical solutions are not yet available. Research has focused on establishing correction factors to account for the matrix error component (derived from comparisons of test results using fresh samples and quality control materials) as well as on developing new analytical systems and quality control materials that can accurately measure both fresh patient and quality control materials.

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[8] J. W. Ross et al., "Matrix Effects and the Accuracy of Cholesterol Analysis," Archives of Pathology and Laboratory Medicine, 117:4 (1993), 393

CAP and CDC Collaborative Study

A recently published CAP and CDC collaborative study examined matrix effects on cholesterol tests.[9] A total of 997 laboratories that participate in the CAP survey were selected (selection method was not specified) to analyze both a freshly frozen serum pool and a lyophilized (freeze-dried) CAP chemistry quality control sample simultaneously, permitting comparisons and bias to be calculated. Laboratories that had submitted incomplete data or had results considered to be outliers (defined in this study as a pooled within-run coefficient of variation across three samples that exceeded 10 percent or a within-run bias of any sample of 25 percent or more relative to the reference method value) were excluded from the analysis.[10] Laboratories that participated in the study were drawn from CAP survey participants, which are mainly hospital laboratories. They are, thus, not representative of small independent laboratories such as those fou in physicians' offices, or even hospitals. While the ability to generalize from this study is limited, the authors make several points that have important consequences for cholesterol measurement.

The CAP and CDC study classified the cholesterol analysis methods into 37 instrumentation and reagent groups. This figure indicates the range of instruments and reagent combinations that regulators must work with in attempting to achieve standardization. Across this group of instruments, they found that "26 (70%) of [the] 37 methods evaluated had statistically significant calibration bias compared with the reference method. The calibration bias of 13 methods (41%) exceeded the NCEP 3% limit for bias."[11] When the investigators adjusted the results to compensate for matrix effects, "92% to 93% of adjusted results met the NCEP 8.9% total error goal relative to the reference method due to superior interlaboratory precision of some of the biased methods."[12] For the fresh-frozen serum sample that was analyzed, test results (N = 900) had a mean bias of 0.1 percent that was nearly identical to the reference method and a coefficient of variation of 4.6 percent, the latter figure slightly exceeding the 1992 NCEP/LSP goal.

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[9] Ross et al., p. 393.

[10] Removing outliers of this magnitude results in a distribution more normal in appearance but has the effect of reducing overall sample variation.

[11] Ross et al., p. 398.

[12] Ross et al., p. 398.

Thus, 70 percent of enzymatic methods used to measure cholesterol in the CAP and CDC study were subject to matrix effects when testing quality control material. The implication of this for NRS/CHOL is that the use of fresh human samples, such as by splitting samples with a member of the National Reference Method Laboratory Network and comparing results, may be a better means to transfer accuracy than the use of processed quality control materials. Given the number of laboratories in the nation and the limited number of National Reference Method Laboratories, this would be a difficult if not impossible task. Table 3.1 lists the 37 instrument and reagent systems and calibration bias relative to the reference method.

Table 3.1: Instrument and Reagent System-Specific Calibration Bias Relative to the Reference Method

Instrument and reagent system	Number of laboratories	Calibration bias
AM Perspective/AM	18	6.3
Olympus Demand/Technicon	7	5.3
Roche Cobas Mira/Roche	29	4.7
Kone Progress/Kone	12	4.6
AM KDA/AM	8	4.5
Baker Encore/Baker	16	3.9
Roche Cobas/Roche	7	3.8
Abbott TDX/Abbott	13	3.0
Baker Centrif/Baker	12	2.3
DuPont Dimension/DuPont	43	2.2
Gilford Impact 400/Ciba	10	2.1[a]
BMD 736, 737/BMD	51	1.8
Baxter Paramax/Paramax	46	1.5
Technicon SMAC/Technicon	17	1.2[a]
Technicon 12-60/Technicon	8	1.1[a]
IL Monarch/IL	32	1.0
Olympus 5000/Olympus	10	0.7[a]
Technicon RA-1000/Technicon	27	0.3[a]
Abbott Spectrum/Abbott	40	0.1[a]
Olympus Demand/Olympus	14	–0.1[a]
Ciba 550 Express/Ciba	10	–0.3[a]
Technicon RA-1000/Sigma	7	–0.3[a]
Technicon Chem 1/Technicon	23	–0.8[a]
DuPont aca/DuPont	18	–1.2
BMD 8700/BMD	15	–1.3[a]
AM Parallel/AM	16	–1.6
BMD 704, 705/BMD	50	–1.6

(continued)

Instrument and reagent system	Number of laboratories	Calibra
AM Parallel/Behring	5	-
BMD 717/BMD	12	-
Ektachem DT 60/Kodak	13	-
Coulter Dacos/Coulter	27	-
Beckman Synchron CX 4,5/Beck	6	-
Abbott VP/Abbott	19	-
Beckman Astra 4,8, Ideal/Beck	52	-
IL Multistat III/Beckman	5	-
Ektachem 400, 700/Kodak	39	-
Electronuclear Gemini/ Electronucl	11	-

*Calibration bias not significant, $p < .05$.

Source: J. W. Ross et al., "Matrix Effects and the Accuracy of Cholesterol Analysis," Archives of Pathology and Laboratory Medicine, 117:4 (1993), 393.

Veterans Affairs Laboratory Study

A study similar to the CAP and CDC investigation was undertaken in 112 VA laboratories in conjunction with CDC.[13] Because VA has the nation's larges hospital system, it provides insight into large-scale efforts to standardize cholesterol measurements. Briefly, the VA research group asked participating laboratories to conduct analyses of fresh serum samples an 1990 CAP quality control materials, permitting comparisons of how well instruments analyzed both types of specimens. This study team found "significant matrix-effect biases with the CAP Survey materials in six of th eight major peer [instrument] groups, despite the fact that accuracy of cholesterol measurements was maintained with fresh serum samples."[14] The authors concluded that "CAP PT [proficiency testing] materials used currently do not behave in a manner identical to fresh human serum whe measuring cholesterol on many, but not all, analytic systems."[15] Table 3.2 presents the study findings.

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[13] There are 174 VA Medical Center outpatient clinics and clinical laboratories that participate in the VA-CDC National Cholesterol Standardization and Certification Program. Of the laboratories in this program, 87 percent had an overall analytic bias of 5 percent or less from the reference method value and 63.2 percent had an overall analytic bias of 3 percent or less.

[14] H. K. Naito et al., "Matrix Effects on Proficiency Testing Materials: Impact on Accuracy of Cholesterol Measurement in Laboratories in the Nation's Largest Hospital System," Archives of Pathology and Laboratory Medicine, 117:4 (1993), 345.

[15] Naito et al., p. 345.

Table 3.2: Matrix Effects for a Group of Instruments Used in VA Medical Center Laboratories

Instrument peer group	Number of laboratories	Bias average (±1 standard deviation in percent)	p[a]
DuPont Dimension	7	–8.9 ± 1.6	0.001
Beckman CX4, CX5, CX7	12	–5.5 ± 1.4	0.001
Kodak Ektachem	47	4.4 ± 2.2	0.001
Instrumentation Laboratory Monarch	5	–3.1 ± 0.8	0.002
Baxter Paramax	7	–2.4 ± 1.0	0.001
Technicon SMAC, RA	10	1.3 ± 1.7	0.05
Hitachi/BMD 707-747	10	0.4 ± 2.2	[b]
Abbott Spectrum, EPX	5	–0.3 ± 1.1	[b]

[a] Student's t test using 2-tailed test indicates the significance of matrix effect biases.

[b] Not significant at the 95-percent confidence level

Source: H. K. Naito et al., "Matrix Effects on Proficiency Testing Materials: Impact on Accuracy of Cholesterol Measurement in Laboratories in the Nation's Largest Hospital System," Archives of Pathology and Laboratory Medicine, 117:4 (1993), 349

The VA study authors noted that the biases that arise from matrix effects will cause incorrect conclusions about the accuracy of laboratory procedures done on fresh patient specimens. Further, matrix effects will "severely hamper interlaboratory accuracy transfer, standardization efforts, and monitoring performance of a laboratory's testing accuracy . . . ."[16]

Accuracy and Precision of Desk-Top Instruments

Cholesterol is often measured with small, portable and semiportable devices called desk-top analyzers, in either a physician's office or a nontraditional setting such as a health fair. Desk-top systems generally use the same kinds of enzymatic methods employed in laboratory settings.

NCEP guidelines do not differentiate between desk-top analyzers and those used in laboratories; all such devices are held to the same overall accuracy standards. A recent study that summarized desk-top analyzers concluded: "In general, desk-top analyzers give fairly accurate measurements on average, but tend to be somewhat more variable than laboratory-based methods in individual samples."[17] The same article links this diffe part to the use of fingerstick blood samples with these analyzers, results of which are likely to differ from venous samples. Other fa that contribute to their measurement variability include lack of op training and use of such devices in field settings where frequent transportation and changes in temperature and humidity can affec results.

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[16] Naito et al., p. 345.

We identified 13 recent studies that evaluated desk-top analyzer performance. We discuss several of these studies in this section, fc on those that permit comparison of data across devices. The first s evaluated five analyzers under tightly controlled conditions: Analy (DuPont), Ektachem DT-60 (Eastman Kodak), Reflotron (Boehringer-Mannheim Diagnostics), Seralyzer (Ames Division, Mi Laboratories), and Vision (Abbott Laboratories). In terms of accur total cholesterol measurements, the Ektachem DT-60 and the o biases of less than 2.0 percent, within the current NCEP bias goal of ≤3 percent. The three other instruments had biases ranging from 5.2 percent to 10.4 percent, thus exceeding the NCEP goal (see table

Table 3.3: Accuracy of Desk-Top Cholesterol Analyzers

Analyze	Value (mmol/L)	Analyst[a]	Kodak Ektachem	Reflotron	Seralyzer
Total cholesterol	5.17	9.7%	1.6%	6.3%	9.8%
	6.21	10.4	1.4	5.2	9.7
HDL cholesterol	0.78	−12.7	6.0		
	1.29	−10.4	6.0		
LDL cholesterol	1.81	−9.6	6.3		
	3.36	18.7	2.2		
	4.14	17.2	1.3		
Triglyceride	1.13	6.0	−5.0		
	1.58	3.6	−3.6		
	2.03	1.7	−2.8		

[a] To convert mmol/L to mg/dL, multiply these values by 38.7. Thus, 5.17 mmol/L equals 200 mg/dL, and 6.21 mmol/L equals 240 mg/dL.

Source: H. W. Kaufman et al., "How Reliably Can Compact Chemistry Analyzers Measure Lip Journal of the American Medical Association, 263.9 (1990), 1247.

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[17] P. S. Bachorik and R. Rock, "Cholesterol Analysis with Desk-Top Analyzers," Methods for Clin Laboratory Measurement of Lipid and Lipoprotein Risk Factors, N. Rifai and G. R. Warnick (eds (Washington, D.C.: AACC Press, 1991), p. 131.

Only three of the five analyzers tested could conduct HDL and LDL cholesterol analyses. Across the three HDL cholesterol levels tested, Kodak Ektachem DT-60 had results that were approximately 6.0-percent higher than the true value while the Analyst and Vision analyses of the low HDL cholesterol measure were −12.7 percent below and 29.7 percent above the true value, respectively. LDL cholesterol measures, derived with the Friedewald equation, conducted on the Kodak Ektachem DT-60 and Vision had an error of less than 3.0 percent while the Analyst exceeded 17 percent at both LDL cholesterol levels tested. The consequence of such error is that the correct total, HDL, and LDL cholesterol value is systematically over- or underestimated.

Data on the precision of these analyzers are presented in table 3.4. Note that the coefficient of variation of the Reflotron and Seralyzer for total cholesterol is 10 percent or higher, exceeding the current NCEP precision goal of ≤ 3 percent.

Table 3.4: Precision of Desk-Top Cholesterol Analyzers[a]

Analyze	Number of pairs	Analyst	Kodak Ektachem	Reflotron	Seralyzer	Vision
Total cholesterol	96					
Mean		6.28	5.79	6.03	6.26	5.77
SD		0.16	0.15	0.80	0.63	0.11
CV%		2.6	2.5	13.3	10.2	2.0
HDL cholesterol	39					
Mean		1.09	1.27			1.34
SD		0.07	0.03			0.12
CV%		6.4	2.5			9.0
LDL cholesterol	39					
Mean		5.25	4.53			4.47
SD		0.21	0.11			0.19
CV%		4.0	2.5			4.3
Triglyceride	39					
Mean		1.59	1.4			1.42
SD		0.08	0.03			0.08
CV%		5.3	2.0			5.2

[a] Neither group has set LDL accuracy standards. Standard deviation (SD) is derived by taking the square root of the variance. With a normal distribution, 68 percent of the values are encompassed by ±1 standard deviation, 95 percent by ±2 standard deviations, and 99.7 percent by ±3 standard deviations. Coefficient of variation (CV) expresses the standard deviation as a percentage of the mean value and is used in clinical chemistry to compare precision at different concentration levels. A method's precision varies inversely with the coefficient of variation: the lower it is, the more precise the method.

Source: H. W. Kaufman et al., "How Reliably Can Compact Chemistry Analyzers Measure Lipids?" Journal of the American Medical Association, 263:9 (1990), 1247.

Another perspective on the data in the preceding tables is how the results could influence the risk category into which a patient is classified (desirable, borderline-high risk, or high risk for coronary heart disease). Two instruments, the Kodak Ektachem DT-60 and Abbott Vision, correctly classified 95 percent and 94 percent of the total cholesterol specimens, respectively. The Analyst, Reflotron, and Seralyzer correctly classified 74 percent, 83 percent, and 75 percent of patient total cholesterol specimens, respectively.

A second study we reviewed that was published in 1993 also evaluated five desk-top devices used to measure cholesterol in screening environments, assessing bias, precision, and patient misclassification error for capillary and venous whole blood and venous plasma. The devices were the Ektachem DT-60 (Kodak), Liposcan (Home Diagnostics), QuickRead (Photest), Reflotron (Boehringer-Mannheim), and Vision (Abbott).[18] The authors concluded that none of these devices met the NCEP performance recommendations regarding bias and precision. Of interest were findings regarding average percentage bias, which differed for capillary and veno whole blood (see table 3.5) and misclassification rates (see table 3.6), which ranged from false negative rates as high as 37 to 48 percent for the Liposcan to false positives up to 38 and 34 percent for the QuickRead. Misclassification into false positive categories was 18 percent for the Vision, 14 percent for the Reflotron, and 7 percent for the Ektachem DT-60.

Table 3.5: Average Percentage Bias for Cholesterol for Four Desk-Top Devices

Device	Capillary blood	Venous blood	Veno plas
Reflotron	4.1%	–0.8%	–
Vision	8.4	4.0	
Kodak DT-60	2.6	[a]	
QuickRead	18.4	16.5	

[a]Not available.

Source: W. G. Miller et al., "Total Error Assessment of Five Methods for Cholesterol Screening," Clinical Chemistry, 39:2 (1993), 299.

Table 3.6: Test Results Misclassified for Five Desk-Top Devices[a]

	Capillary blood		Venous blood		Venous plasma	
Device	False negative	False positive	False negative	False positive	False negative	False positi
Reflotron	2.2%	14.1%	7.1%	3.1%	2.1%	4
Vision	0	18.3	0	5.7	0	5
DT-60	4.4	6.7	[b]	[b]	2.0	5
QuickRead	0	37.5	0	34.0	1.6	11
Liposcan	36.8	2.6	47.5	0	[b]	

[a]False negative refers to a test result reported to the patient that is incorrectly low. A patient in this situation may not be treated but should be considered, according to NCEP guidelines. False positive refers to a test result reported to the patient that is incorrectly high. In this situation, a person may be treated when that is unnecessary, according to NCEP guidelines.

[b]Not available.

Source: W. G. Miller et al., "Total Error Assessment of Five Methods for Cholesterol Screening," Clinical Chemistry, 39:2 (1993), 300.

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[18] W. G. Miller et al., "Total Error Assessment of Five Methods for Cholesterol Screening," Clinical Chemistry, 39:2 (1993), 297-304.

Home Test Devices

Home test kits to measure total cholesterol have also been cleared by FDA and have recently begun to be marketed directly to consumers (they have been available to physicians since 1991). Total cholesterol results obtained with the AccuMeter, currently the only such device being marketed in the United States, for 100 patients were compared with a CDC-standardized laboratory at the Medical College of Virginia.[19] While AccuMeter's results met NCEP guidelines for measurement bias (≤3 percent) for both capillary and venous blood when using a mean bias measure, these researchers found that mean absolute percentage bias was 5.7 percent and 5.2 percent, respectively.[20] In addition, 18 to 20 percent of samples fell outside the ±8.9 percent of the reference result, the level the NCEP established for acceptable total error for single cholesterol measurements. Figures for precision, from 40 total cholesterol assays done in duplicate from three pools of human serum with mean concentrations of 182 mg/dL, 223 mg/dL, and 266 mg/dL, exceeded NCEP/LSP guidelines (≤3 percent precision error); the coefficients of variation were 4.5 percent, 5.4 percent, and 5.8 percen respectively. The authors noted that approximately 5 percent of the devices did not function properly and could not provide a cholesterol reading.

We met with FDA officials to discuss their decision to permit marketing of the AccuMeter under 510(k) regulations. They explained that it met the criteria of "substantial equivalence" to an analyzer currently being marketed, therefore complying with existing regulations, although the device does not meet NCEP standards for precision and accuracy (as judged by "traceability" to the Abell-Kendall reference method).

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[19] J. McKenney and W. G. Miller, "A Perspective on Home Cholesterol Testing," *The Fats of Life*, 7:4 (1993), 1-7.

[20] The mean bias measure reflects the average difference from the reference value, taking into consideration negative and positive differences; the mean absolute bias measure does not take into account negative and positive differences and reflects the average of the absolute difference from the reference value.

Chapter 4

Factors That Influence the Variability of Cholesterol Levels

Even if a single cholesterol measurement were analytically accurate and precise, it would not reflect how a person's cholesterol can vary from day to day. Total, HDL, and LDL cholesterol levels vary over time and are influenced by what are termed preanalytic or biological factors that include behavioral (exercise, diet, alcohol consumption), clinical (disease pregnancy), and sample collection conditions. In this chapter, we answer our third evaluation question: What factors influence cholesterol levels?

Scientific literature indicates that some variation and fluctuation of an individual's total, HDL, and LDL cholesterol is normal and to be expected. For instance, in some individuals, week-to-week fluctuations can be dramatic while in others virtually no change may occur over the same tim period. Overall, biological variation of total cholesterol is reported to average 6.1 percent; HDL cholesterol variation averages 7.4 percent; LDL biological variability, 9.5 percent; triglycerides, 22.6 percent. These findings suggest that variation in cholesterol levels is normal and, for som individuals, can be quite pronounced. The implication for testing, particularly for patients near a cutpoint (such as 240 mg/dL) is that repeated measurements may be necessary. In light of measurement uncertainty for HDL and LDL, multiple measures of these subfractions may be warranted, particularly before making a diagnosis.

Other factors—diet, exercise, alcohol intake—appear to have differing effects on individuals' cholesterol levels. The amount of the effect varies depending on the amount and duration of intake and physiological factors In some, it may not have a large effect on total and LDL cholesterol levels. This may be partially related to the estimates that one third of an individual's cholesterol level is linked to diet while the body produces the remaining two thirds. The evidence regarding regular exercise points to the benefits associated with such activity, as measured by changes in lipid levels. While alcohol intake can have a positive effect on cholesterol levels, consumption must be balanced with the potential risks associated with it. The potential effect of diet on cholesterol levels was noted in the 1990 NCEP report on cholesterol measurement, which recommended that patients maintain their usual diet and that their weight be stable for at least 2 weeks before their cholesterol level is measured.

Clinical factors such as disease, pregnancy, and some medications (diuretics, beta blockers, oral contraceptives) can also alter cholesterol levels. How a blood specimen is taken can also have a crucial role in cholesterol analysis. Some research has found that fingerstick (capillary) samples differed markedly from venous samples when analyzed by the same device while other researchers have called for more standardized specimen collection techniques.

Biological Variation

Cholesterol levels within a person vary over time, depending on a number of factors. As discussed in chapter 1, for example, as people age, their total cholesterol level tends to increase. However, cholesterol levels can also vary considerably between measurements because of what is termed intra-individual biological variability—that is, normal fluctuations in cholesterol levels are estimated to account for about 65 percent of the total intra-individual variation for both total and HDL cholesterol and about 95 percent of the variation for triglycerides. Studies have linked other types of biological variation to diet, alcohol intake, smoking, and physical activity. The body of literature on this subject is large: a 1992 article reviewed more than 300 publications, most of which had been published within the previous 5 years.[1]

A recent statistical synthesis of findings from 30 studies published between 1970 and 1992 provides considerable information on intra-individual biological variation—that is, the normal fluctuation in cholesterol levels referred to above. According to this review, total cholesterol is the most stable lipid, with the day-to-day biological variation averaging 6.1 percent; variations in HDL cholesterol concentrations, 7.4 percent; LDL biological variability, 9.5 percent; triglyceride, 22.6 percent.[2]

The number of subjects in the selected studies of total cholesterol variability ranged from small (less than 20) to quite large (14,600). Not surprisingly, the number of specimens and the sampling intervals varied as well. Two large studies analyzed two specimens, taken 1 month apart, while another study with a smaller number of subjects analyzed specimens taken twice a week for 10 weeks. Results for HDL variability were based on 16 studies, triglyceride variability 19 studies, and LDL variation 10 studies.

Two recent articles have also reported similar findings. One study compared total cholesterol and HDL measurements taken from 40 male subjects 1 week apart. The authors found a relatively wide range of variability in some patients: one patient's total cholesterol declined dramatically from one week to the next, dropping from nearly 300 mg/dL to just over 220 mg/dL, while several others' total cholesterol level scarce moved between the two tests (the coefficient of variation for single measurements was 6.8 percent for total cholesterol and 10.5 percent for HDL, slightly higher than the figures from the statistical synthesis reported earlier).[3]

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[1] G. R. Cooper et al., "Blood Lipid Measurements: Variations and Practical Utility," Journal of the American Medical Association, 267:12 (1992), 1652-59.

[2] S. J. Smith et al., "Biological Variability in Concentrations of Serum Lipids: Sources of Variation among Results from Published Studies and Composite Predicted Values," Clinical Chemistry, 39:6 (1993), 1012-22.

Another study of cholesterol variability tracked 20 subjects 22 to 63 years old measuring their total, LDL, and HDL cholesterol weekly for 4 weeks. The authors found variations of more than ±20 percent in the serum levels of total cholesterol, LDL, and HDL in 75 percent, 95 percent, and 65 percent of the subjects, respectively. More important, 40 percent moved in or out of one of the risk categories, and 10 percent moved two categories—from "desirable" to "high risk."[4]

Other research has found that LDL and total cholesterol levels within individuals vary by season, both averaging 2.5-percent higher in the winter than the summer. The HDL cholesterol level, however, has not been found to vary seasonally. Women are affected by another aspect of biological variability; total cholesterol concentrations may average 20 percent lower during the luteal phase (the period immediately after ovulation) of the menstrual cycle.

Behavioral Factors

Cholesterol levels vary because of behavioral factors, and some of this variability can influence short-term measurements. For example, strenuous exercise 24 hours prior to having a blood specimen taken can elevate an individual's HDL cholesterol level. Likewise, moderate alcohol consumption can increase HDL and decrease LDL cholesterol levels. Behavior over longer periods of time can also affect cholesterol levels—diet, alcohol consumption, exercise. The relevance to the measurement theme of this report is that there is more to variation in cholesterol levels than inaccurate laboratory tests.

Diet and Cholesterol

Consumption of certain saturated fatty acids and, to a lesser extent, cholesterol is linked to higher serum LDL cholesterol values. In terms of diet, an increase in cholesterol intake of about 100 mg (per 4,200 joules raises plasma cholesterol by about 10 mg/dL. Progressively higher cholesterol intakes exceeding 500 mg appear to have smaller increment effects on cholesterol levels.[5] The same study points out that dietary cholesterol is incompletely and variably absorbed by individuals, rangin from 18 to 75 percent. Further, people with the highest LDL cholesterol levels appear to have the highest percentage of absorption of dietary cholesterol.

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[3] R. H. Christenson et al., "Improving the Reliability of Total and High-Density Lipoprotein Cholesterol Measurements," Archives of Pathology and Laboratory Medicine, 116 (1991), 1212-16.

[4] M. Mogadam et al., "Within-Person Fluctuations of Serum Cholesterol and Lipoproteins," Archives of Internal Medicine, 150 (1990), 1645-48.

How individuals respond to different diets varies, however. One recent synthesis of literature on diet and health points out that

> "blood cholesterol responses of individuals differ substantially in response to changes in dietary lipids .... For the same increase in dietary cholesterol or saturated fat, the cholesterol levels of most persons will increase, but some will remain essentially unchanged and a few will increase dramatically."[6]

As noted in chapter 2, only one third of an individual's cholesterol is derived from diet and the remaining two thirds are manufactured by the liver.

In terms of the contribution that diet can make to cholesterol reduction, the 1993 NCEP guidelines state that men who follow the step I diet could expect their total cholesterol level to be reduced 5 to 7 percent while tho who follow the more restrictive step II could expect an 8-to-14 percent reduction. These estimates are based on models derived from metabolic ward studies (done on institutionalized patients), which closely monitore and controlled individuals' adherence to their diet. Some researchers hav noted that such reductions can be difficult to achieve in a "free living" population.

Alcohol Intake

Published epidemiological studies have demonstrated a relationship between alcohol intake and changes in cholesterol profiles. The amount o change attributed to alcohol depends on the amount consumed, individual susceptibility, genetic variables, and diet. Moderate alcohol intake (defined as several drinks a day) appears to increase HDL cholesterol and may be associated with reduced risk of coronary heart disease. Greater alcohol consumption is also associated with a lowering of LDL cholesterol and an increase in triglycerides. In one study, it is estimated that 4 to

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[5] G. R. Cooper et al., p. 1653.

[6] Walter Willett, Nutritional Epidemiology (New York: Oxford University Press, 1990), p. 362.

6 percent of the variance of HDL cholesterol levels in the population may b linked to alcohol consumption.

Exercise

Exercise has been shown to influence cholesterol levels and has received increased attention as having a preventive effect on coronary heart disease. Researchers have found that exercise that is strenuous and promotes endurance causes LDL, triglycerides, and apo B to decrease whil raising HDL and apo AI levels. Other evidence regarding exercise points to the benefits of brisk walking. One study found that previously sedentary women who walked an average of 155 minutes per week decreased their total cholesterol level by 6.5 percent compared with a decrease of 2.2 percent in control subjects, and the HDL level of walkers increased 27 percent, compared with a 2-percent increase in controls.[7] A recent article suggests that the effect of these changes depends on the volume, intensity, and type of exercise undertaken, a slight variation on earlier work.[8]

Apart from longer-term effects, acute exercise also causes a significant rise in HDL levels such that it is recommended that patients avoid any strenuous exercise 24 hours prior to having a blood specimen taken.[9]

Obesity

Obese individuals have been found to have higher total and LDL cholestero and triglyceride levels and lower HDL cholesterol when compared to nonobese members of control groups. When an obese individual loses weight, a decline in triglyceride level occurs (about 40 percent); total and LDL cholesterol levels are found to decline about 10 percent while the HDL level increases about 10 percent. The implication for cholesterol measurements, particularly for obese individuals who repeatedly gain and lose weight, is that such fluctuations can be the source of significant variation in lipoprotein levels.[10] In fact, NCEP/LSP recommended that an individual's weight be stable and that he or she maintain his or her usual diet for at least 2 weeks prior to having cholesterol measured.[11]

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[7] A. E. Hardman et al., "Brisk Walking and Plasma High-Density Lipoprotein Cholesterol Concentra in Previously Sedentary Women," British Medical Journal, 299 (1989), 1204-9.

[8] P. A. Taylor and A. Ward, "Women, High-Density Lipoprotein Cholesterol, and Exercise," Archives Internal Medicine, 153 (1993), 1178-84

[9] N. Rifai et al., "Preanalytical Variations in Lipid, Lipoprotein, and Apolipoprotein Testing," in Meth for Clinical Laboratory Measurement of Lipid and Lipoprotein Risk Factors, N. Rifai and G. R. War (eds.) (Washington, D.C.: AACC Press, 1991), p. 23.

[10] Cooper et al., p. 1653.

Clinical Factors

A person's cholesterol profile can be affected by acute, infectious, and metabolic diseases, and some types of medications have been linked with elevated levels in some patient groups.

Disease

Several conditions are associated with increased cholesterol levels. Diabetes mellitus and hypothyroidism are cited as the most common of these, with total cholesterol and LDL cholesterol levels being elevated in 30 percent of the patients with the latter condition. Patients with diabetes mellitus sometimes have elevated triglycerides, and higher levels of insulin are positively associated with unfavorable levels of total and LDL cholesterol, triglycerides, apo B, and blood pressure, and negatively with HDL cholesterol components.

Acute myocardial infarction is associated with decreases in levels of total cholesterol, LDL, apo AI, and apo B. Indeed, lipid levels after a heart attack are affected to such a degree that it is recommended that blood specimens be obtained within 24 hours of the event; if they cannot be taken within 24 hours, then they should not be taken for 3 months because the test will not accurately reflect the patient's usual lipid level. Other diseases such as Tay-Sachs, rheumatoid arthritis, and infections can also alter lipid profiles.[12] In addition, familial hypercholesterolemia and other related disorders are associated with increased blood cholesterol levels.

Drug-Induced Variations and Pregnancy

Medication can also alter lipid levels. Diuretics, some beta blockers, and sex steroids have been cited as changing lipid levels. Oral contraceptives high in progestin can increase serum total and LDL cholesterol and decrease HDL cholesterol levels, while contraceptives with high estrogen content can cause opposite changes. Similar changes have been found in postmenopausal women taking estrogen supplements.[13]

Pregnancy is associated with changes in lipid profiles in the second and third trimesters, when total and LDL cholesterol, triglyceride, apo AI, apo

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[11] National Cholesterol Education Program, Recommendations for Improving Cholesterol Measurement (Bethesda, Md.: 1990).

[12] Rifai et al., p. 23.

[13] Rifai et al., p. 24

AII, and apo B are significantly increased. Because of these changes, lipid levels are affected to the degree that testing is not recommended until 3 months postpartum or 3 months following cessation of lactation.

Laboratory Factors

How a blood specimen is collected and handled may affect lipid levels. For example, blood cholesterol samples are often drawn when the patient is in a fasting state, particularly when a lipid profile is to be taken. This is because eating a typical fat-containing meal causes a patient's lipid profile to change, an effect that lasts about 9 hours. Typically, triglyceride levels increase as does very-low-density lipoprotein (VLDL), while LDL cholesterol falls significantly.

The source of the blood specimen taken can also influence measured cholesterol levels. Here the issue of concern is whether the sample source is capillary (taken from a finger) or venous (taken from a vein). One large research study found that capillary blood total cholesterol was approximately 7-percent higher than venous blood samples when both were analyzed with the same analyzer. According to this same study,

> "the most reliable screening measurements were obtained when the analyses were performed in venous plasma samples by a qualified clinical laboratory. . . . The most-variable measurements were obtained with the capillary samples, and these measurements seemed to be most prone to misclassification overall."[14]

A 1993 article briefly discusses the difference between venous and capillary samples, pointing out "contradictory results" (that is, some studies reporting either higher or lower capillary results than venous results, depending on the various procedures and devices tested) and a lack of consensus in the literature about such differences. The study's authors conclude that "capillary collection technique is critical and must be standardized to obtain reliable cholesterol results."[15]

How the specimen is taken and prepared for analysis also can affect lipid level measurements. Here factors such as the knowledge and experience of the laboratory technician are important. For example, the length of time a person is sitting or standing prior to having the specimen taken has been demonstrated to influence cholesterol test results. Patients should remain seated for at least 15 minutes before a venous sample is taken, and if a tourniquet is used, it should be applied for less than 1 minute before the specimen used for a lipid analysis is taken.[16] Proper storage of samples i also important to avoid changes in the composition of samples and to ensure accurate measurement results. Use of a standard collection polic by trained laboratory technicians can help minimize variability associate with these factors.

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[14] P. S. Bachorik et al., "Cholesterol Screening: Comparative Evaluation of On-Site and Laboratory-Based Measurements," Clinical Chemistry, 36:2 (1990), 259.

[15] G. W. Miller et al., "Total Error Assessment of Five Methods for Cholesterol Screening," Clinical Chemistry, 39:2 (1993), 302.

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[16] Rifai et al., p. 27.

Chapter 6

The Potential Effect of Measurement Uncertainty and Agency Comments and Our Response

In this chapter, we discuss the study's fourth evaluation question: What i the potential effect of uncertain measurement? This is followed by our conclusions and discussion of agency comments.

Addressing Measurement Error

Progress has been made in improving analytical accuracy in cholesterol measurement, with the development of better methods and materials in recent years. Yet, despite the attention cholesterol has received, it continues to be difficult to measure with accuracy and consistency acros the broad range of devices and settings in which it is analyzed. While several studies have found that accuracy with patient samples was good, problems with matrix effects from using processed quality control materials have occurred, thus making it difficult to adequately assess accuracy among laboratories. In addition, the lack of information on accuracy in many laboratory settings where patients are likely to be test such as commercial laboratories, physicians' offices, and mass screening locations, makes it impossible to know whether the accuracy goals established for total and HDL cholesterol are uniformly being met.

Even if one could be certain that a laboratory could provide reasonably accurate and precise test results, biological and behavioral factors such diet, excercise, or illness cause an individual's cholesterol level to vary. I has been estimated that such factors may account for up to 65 percent o the total variation in an individual's reported cholesterol measurement. Studies have documented that some individuals' cholesterol level can va dramatically from week to week while others' remains relatively constan Although some biological variation can be controlled for, by having patients maintain their weight and diet for a modest period prior to measurement, many factors cannot be controlled.

Total error from both analytical and biological variability can be considerable, as shown in tables 5.1 and 5.2, where calculations are mad for hypothetical total and HDL cholesterol test results at different specifi levels. For the purposes of this analysis, which is intended to illustrate t potential range of variability around an actual or known cholesterol leve we used the current goals for total analytical error (±8.9 percent for tota cholesterol according to NCEP and ±30 percent for HDL according to HCFA and what is currently known about biological variability from a synthesi of studies (6.1 percent for total cholesterol and 7.4 percent for HDL cholesterol). Both analytical and biological variability can of course be lower or higher than these figures, depending on a combination of factor

Table 5.1: The Effect of Analytical and Biological Variability on Total Cholesterol Test Results[a]

	Potential range		
Test result	Based on analytical variability alone[b]	Based on biological variability alone[c]	Based on variat
180	164-196	158-202	15
200	182-218	176-224	16
220	200-240	193-247	18
240	219-261	211-269	201
260	237-283	228-292	21

[a] Values are mg/dL.

[b] Calculated using the NCEP Laboratory Standardization Panel goal of ±8.9 percent (0.05 level, 2-tailed test). The total analytic error of 8.9 percent is derived by summing the precision and bia components in the following manner:

$$3 + 1.96\sqrt{3^2}.$$

[c] Calculated using an estimate of intraindividual biological variability (6.1 percent coefficient of variation) derived from a meta-analysis of 30 studies by S. J. Smith et al., "Biological Variability i Concentrations of Serum Lipids: Sources of Variation Among Results from Published Studies an Composite Predicted Values," Clinical Chemistry, 39·6 (1993).

[d] Total percentage error calculated from the following expression:

$$3 + 1.96\sqrt{3^2 + 6.1^2}.$$

Table 5.2: The Effect of Analytical and Biological Variability on HDL Cholesterol Test Results[a]

	Potential range		
Test result	Based on analytical variability alone[b]	Based on biological variability alone[c]	Based on variab
15	11-20	13-17	10
25	18-33	21-29	17
35	25-46	30-40	24
45	32-59	38-52	31
55	39-72	47-63	38

[a] Values are mg/dL.

[b] Calculated using the HCFA goal of ±30 percent.

[c] Calculated using an estimate of intraindividual biological variability (7.4 percent coefficient of variation) derived from a meta-analysis of 16 studies by S. J. Smith et al., "Biological Variability in Concentrations of Serum Lipids: Sources of Variation among Results from Published Studies and Composite Predicted Values," Clinical Chemistry, 39.6 (1993).

[d] Calculated as the square root of the sum of analytical variability squared plus biological variability squared (30.9 percent).

The results in tables 5.1 and 5.2 show that a single cholesterol measurement may be highly misleading with respect to an individual's actual cholesterol value. A total cholesterol value that is known to be 2 mg/dL, for example, may vary as much as 16 percent or range from 201 279 mg/dL, when using these error rate assumptions. Similar estimates HDL cholesterol measurements are presented in table 5.2.

The implication of these estimates is that cholesterol levels should be thought of in terms of ranges rather than absolute fixed numbers. Compensating for variation by using the average of at least two cholest measurements is in line with the current NCEP guidelines and recent literature on the subject.[1] The most recent NCEP Adult Treatment Panel recommends that a second test be done when an initial measurement h found that total cholesterol exceeds 200 mg/dL and HDL is under 35 mg/ In terms of HDL and LDL cholesterol, which have been documented to ha analytical and biological variation somewhat higher than total choleste more variability can be expected. CDC officials we interviewed emphasi that considerable scientific work remains before HDL measurement is a well understood as total cholesterol. Authors of a recent study in Clinic Chemistry therefore recommend that as many as four HDL and LDL cholesterol tests be done before making treatment decisions.[2]

A practical way to address the problem of measurement variability is to compare multiple tests using a technique termed "relative range."[3] Rela range is calculated by dividing the range—the difference between two values—by the mean. For example, if a patient has two total cholestero results of 240 and 200 mg/dL, you would divide 40 by 220 to determine t relative range, which is 0.18. The relative range, according to the researchers who developed this method, should be less than or equal to 0.16 for two specimens. For the example just given, a third test would b needed, and the goal would be to achieve a relative range of less than o equal to 0.19; with four specimens, the relative range should be less th or equal to 0.21.[4]

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[1] The effect of a second test on the range of variability around a known cholesterol level can be illustrated with our previous hypothetical example, in which analytical and biological variability ar combined. For a total cholesterol value of 240 mg/dL, the total percentage error would be about 12 percent when factoring in a second measurement, thus narrowing the variability to a range of 21 270 mg/dL.

[2] S. J. Smith et al., "Biological Variability in Concentrations of Serum Lipids: Sources of Variation among Results from Published Studies and Composite Predicted Values," Clinical Chemistry, 39:6 (1993), 1021.

[3] G. R. Cooper et al., "Estimating and Minimizing Effects of Biologic Sources of Variation by Relati -Range when Measuring the Mean of Serum Lipids and Lipoproteins," Clinical Chemistry, 40:2 (1994 227-32.

Implications of Measurement Variability

Having accurate and precise cholesterol measurements is important, g the central role that cholesterol measurement has in classifying, evaluating, and treating patients deemed at risk of coronary heart dise As noted in chapter 1, the average total cholesterol level for U.S. adult years old and older is about 205 mg/dL, which puts them within the NCEP-defined borderline-high risk category. Moreover, 29 percent of U. adults, 52 million people, have a cholesterol level that is classified as t high, making them candidates for dietary therapy. Of this group, an estimated 12.7 million adults, one third of whom have established coronary heart disease, might be considered candidates for drug thera to lower their cholesterol level. Once drug therapy is initiated, it may n to be maintained for life.

Although the NCEP guidelines recognize the problem of measurement variability and the guidelines stress the need for multiple measurement important consequences can be associated with measurement error. Th potential exists, for example, that physicians may not account for measurement problems and may base decisions about patients on incorrect test results. In a worst-case scenario, two types of diagnostic errors could occur: false-positive or false-negative screens. A false-posi screen could result in treating individuals who in fact have a desirable total, HDL, and LDL cholesterol level. A false-negative result would incorrectly reassure an individual that his or her cholesterol level is lo The risk of misclassification would be greatest for those whose measur cholesterol levels are closest to one of the cutpoints. There is less ambiguity when values are well above or below a cutpoint. The likeliho of such errors occurring, however, is greater if physicians rely on only single cholesterol measurement in making treatment decisions.

Continuing efforts are needed to improve the accuracy and precision o lipid measurements so that medical decisions to initiate and continue treatment to lower elevated cholesterol levels can be both effective and efficient. To minimize misclassification problems, it is also important to ensure that physicians who evaluate and treat patients with elevated cholesterol levels are knowledgeable about measurement variability an the need to conduct multiple tests.

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[4] For further information on relative range, see G. R. Cooper et al., "Blood Lipid Measurements: Variations and Practical Utility," Journal of the American Medical Association, 267:12 (1992), 1652-

Agency Comments and Our Response

Officials from HHS reviewed a draft of this report and provided written comments, reproduced in appendix I. In addition, HHS provided draft technical comments that we have incorporated in the text where appropriate.

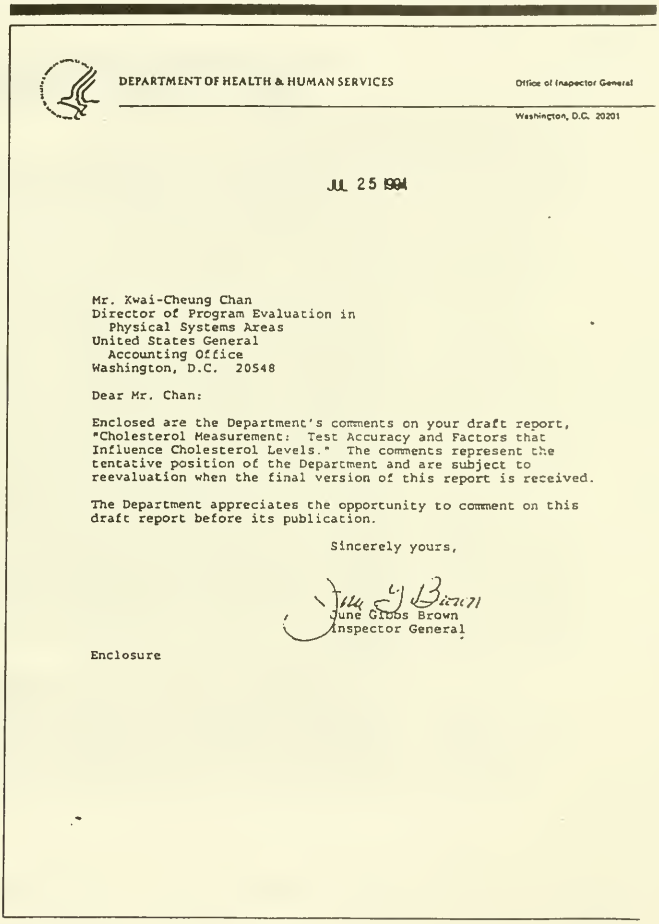
Overall, HHS officials believed that cholesterol measurement has improved substantially in recent years and that accuracy in laboratories across the country is better than what is presented in our report. Regarding general comments on the need for better standardization materials (lyophilized serum pools without matrix effects), we agree that this is a major challenge that must be addressed if measurement is to be improved. This point was made in NCEP's 1990 report on cholesterol measurement, indicating that this is not a new problem but rather one that was noted previously.

HHS did not concur with a recommendation we included in the draft report concerning an assessment of whether problems of patient "misclassification" result from measurement variability. It indicated that information on misclassification already exists and that additional work would only provide further definition of the issue rather than solving known problems such as the effect of matrix effects on measurement accuracy. We recognize that some information on this issue does exist and also understand that further efforts are currently under way, particularly by NIH and CDC, to assess how the NCEP guidelines are being implemented in practice and to evaluate overall laboratory performance. We have deleted our draft recommendation from the final report because these ongoing agency efforts should respond to our concerns about misclassification. We encourage HHS to continue this work and provide the results to the Congress and the general public.

The agency also suggested that the discussion of diet and clinical trials that we included in the draft was too brief. We have deleted this discussion from the final report and will address it in more depth in a later report we are preparing on the clinical trial base of information that supports the NCEP guidelines.

Appendix I

Comments From HHS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

JUL 25 1994

Mr. Kwai-Cheung Chan
Director of Program Evaluation in
Physical Systems Areas
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Chan:

Enclosed are the Department's comments on your draft report, "Cholesterol Measurement: Test Accuracy and Factors that Influence Cholesterol Levels." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

June G. Brown

June Gibbs Brown
Inspector General

Enclosure

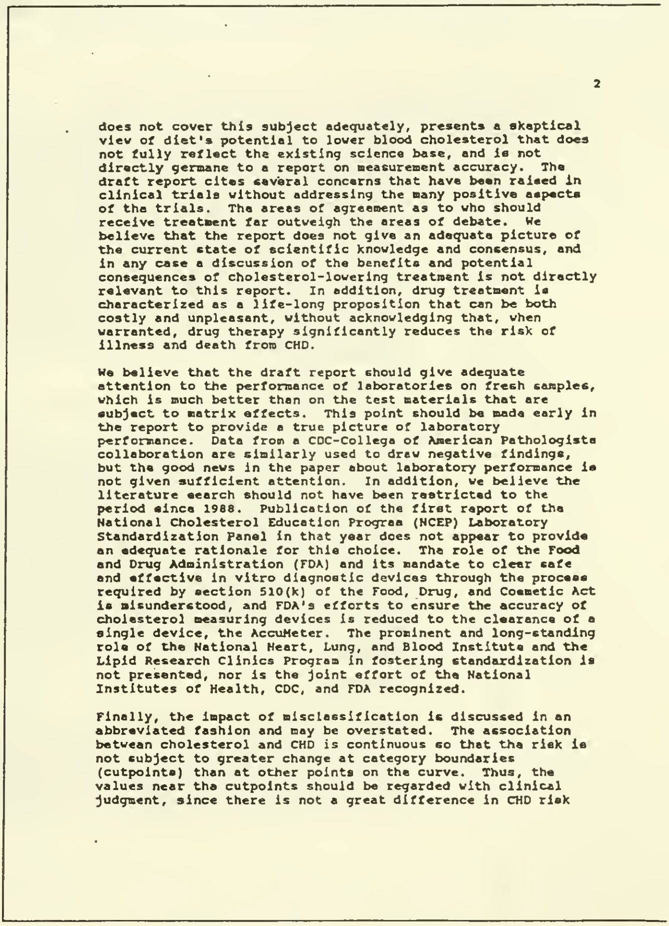
COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE (GAO) DRAFT REPORT "CHOLESTEROL MEASUREMENT: TEST ACCURACY AND FACTORS THAT INFLUENCE CHOLESTEROL LEVELS"

General Comments

The GAO draft report correctly identifies the problem of matrix effects to be an important factor in the accuracy problem of cholesterol testing. The draft report's proposed recommendation calls for assessing in greater detail how much misclassification of patients into risk categories is now occurring, rather than a solution.

We believe the usefulness of the report would be increased if GAO would describe the resources that will be needed to resolve the problems identified. Standardization resources, such as lyophilized serum pools without matrix effects for total cholesterol, low-density lipoprotein (LDL) cholesterol (bad cholesterol), high-density lipoprotein (HDL) cholesterol (good cholesterol) and triglycerides, will have to be developed to assure accurate measurements in clinical laboratories. The reference methods used by the Centers for Disease Control and Prevention (CDC) for HDL cholesterol, LDL cholesterol, and triglycerides need to be documented and checked for transferability in order for them to become acceptable as national and international reference methods. The CDC-used reference method for LDL cholesterol can attain a CV (precision) of 1.2 percent, for HDL cholesterol a CV of 2.2 percent, for very-LDL cholesterol a CV of 12 percent and for triglycerides a CV of 3 percent. These values are highly acceptable for a reference method, but still must be documented for acceptance by the USA-National Committee for Clinical Laboratory Standards and the World Health Organization. Clinical laboratories will have difficulty in fully meeting the requirements of standardization and proficiency testing programs, and the Health Care Financing Administration evaluation of the Clinical Laboratory Improvement Amendments' requirements for cholesterol and related lipoprotein measurements will be impeded, until a lyophilized serum free of matrix effects becomes available to evaluate and monitor cholesterol measurements in clinical laboratories.

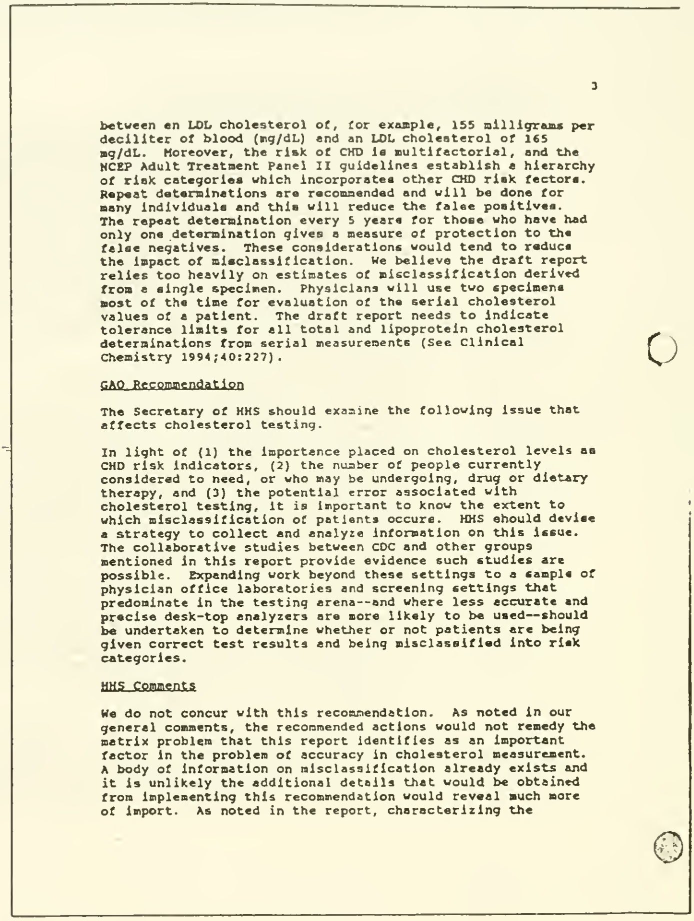
A second problematic element of the draft report is that it generally presents the negative aspects of the areas of diet and clinical trials while neglecting much positive information. We believe the draft report's discussions on diet and clinical trials could be deleted from this report and a balanced presentation included in the GAO's upcoming report on the cholesterol science base. We believe the draft report's discussion on diet and coronary heart disease (CHD)



does not cover this subject adequately, presents a skeptical view of diet's potential to lower blood cholesterol that does not fully reflect the existing science base, and is not directly germane to a report on measurement accuracy. The draft report cites several concerns that have been raised in clinical trials without addressing the many positive aspects of the trials. The areas of agreement as to who should receive treatment far outweigh the areas of debate. We believe that the report does not give an adequate picture of the current state of scientific knowledge and consensus, and in any case a discussion of the benefits and potential consequences of cholesterol-lowering treatment is not directly relevant to this report. In addition, drug treatment is characterized as a life-long proposition that can be both costly and unpleasant, without acknowledging that, when warranted, drug therapy significantly reduces the risk of illness and death from CHD.

We believe that the draft report should give adequate attention to the performance of laboratories on fresh samples, which is much better than on the test materials that are subject to matrix effects. This point should be made early in the report to provide a true picture of laboratory performance. Data from a CDC-College of American Pathologists collaboration are similarly used to draw negative findings, but the good news in the paper about laboratory performance is not given sufficient attention. In addition, we believe the literature search should not have been restricted to the period since 1988. Publication of the first report of the National Cholesterol Education Program (NCEP) Laboratory Standardization Panel in that year does not appear to provide an adequate rationale for this choice. The role of the Food and Drug Administration (FDA) and its mandate to clear safe and effective in vitro diagnostic devices through the process required by section 510(k) of the Food, Drug, and Cosmetic Act is misunderstood, and FDA's efforts to ensure the accuracy of cholesterol measuring devices is reduced to the clearance of a single device, the AccuMeter. The prominent and long-standing role of the National Heart, Lung, and Blood Institute and the Lipid Research Clinics Program in fostering standardization is not presented, nor is the joint effort of the National Institutes of Health, CDC, and FDA recognized.

Finally, the impact of misclassification is discussed in an abbreviated fashion and may be overstated. The association between cholesterol and CHD is continuous so that the risk is not subject to greater change at category boundaries (cutpoints) than at other points on the curve. Thus, the values near the cutpoints should be regarded with clinical judgment, since there is not a great difference in CHD risk



between an LDL cholesterol of, for example, 155 milligrams per deciliter of blood (mg/dL) and an LDL cholesterol of 165 mg/dL. Moreover, the risk of CHD is multifactorial, and the NCEP Adult Treatment Panel II guidelines establish a hierarchy of risk categories which incorporates other CHD risk factors. Repeat determinations are recommended and will be done for many individuals and this will reduce the false positives. The repeat determination every 5 years for those who have had only one determination gives a measure of protection to the false negatives. These considerations would tend to reduce the impact of misclassification. We believe the draft report relies too heavily on estimates of misclassification derived from a single specimen. Physicians will use two specimens most of the time for evaluation of the serial cholesterol values of a patient. The draft report needs to indicate tolerance limits for all total and lipoprotein cholesterol determinations from serial measurements (See Clinical Chemistry 1994;40:227).

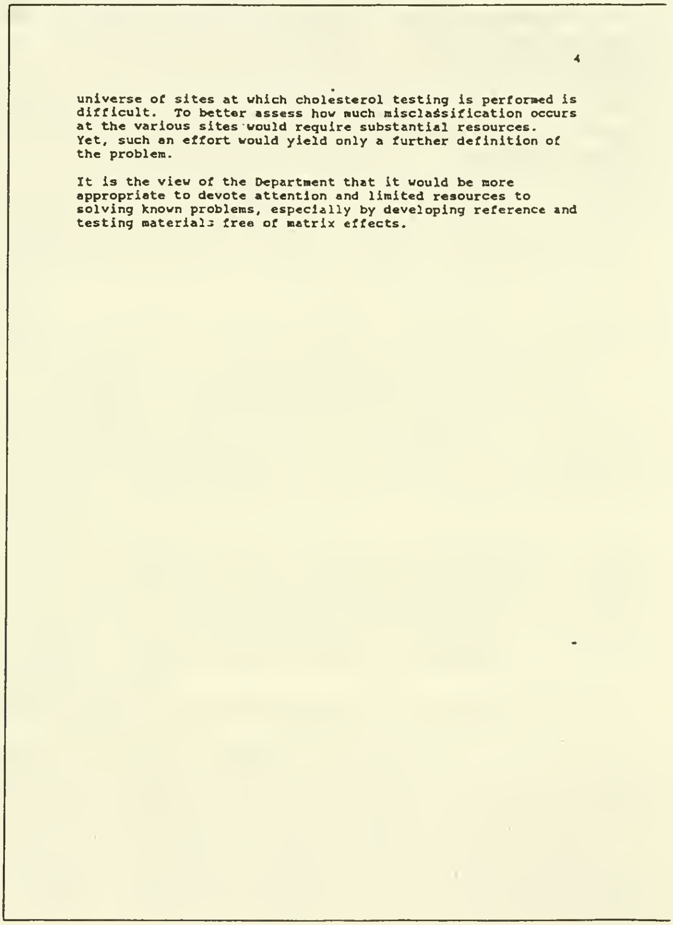
GAO Recommendation

The Secretary of HHS should examine the following issue that affects cholesterol testing.

In light of (1) the importance placed on cholesterol levels as CHD risk indicators, (2) the number of people currently considered to need, or who may be undergoing, drug or dietary therapy, and (3) the potential error associated with cholesterol testing, it is important to know the extent to which misclassification of patients occurs. HHS should devise a strategy to collect and analyze information on this issue. The collaborative studies between CDC and other groups mentioned in this report provide evidence such studies are possible. Expanding work beyond these settings to a sample of physician office laboratories and screening settings that predominate in the testing arena--and where less accurate and precise desk-top analyzers are more likely to be used--should be undertaken to determine whether or not patients are being given correct test results and being misclassified into risk categories.

HHS Comments

We do not concur with this recommendation. As noted in our general comments, the recommended actions would not remedy the matrix problem that this report identifies as an important factor in the problem of accuracy in cholesterol measurement. A body of information on misclassification already exists and it is unlikely the additional details that would be obtained from implementing this recommendation would reveal much more of import. As noted in the report, characterizing the



universe of sites at which cholesterol testing is performed is difficult. To better assess how much misclassification occurs at the various sites would require substantial resources. Yet, such an effort would yield only a further definition of the problem.

It is the view of the Department that it would be more appropriate to devote attention and limited resources to solving known problems, especially by developing reference and testing materials free of matrix effects.

Appendix II

Major Contributors to This Report

Program Evaluation and Methodology Division	John E. Oppenheim, Assistant Director Phillip R. Herr, Project Manager
Denver Regional Office	Debra J. Carr, Senior Evaluator

Mrs. MORELLA. Thank you very much, Mr. Chan. We will have some questions for you in a bit.

Before I present Dr. Lenfant, I just wanted to recognize that we have been joined by another Member of the subcommittee, Congresswoman Zoe Lofgren from California. I did not know whether you would want to make any comments now?

Ms. LOFGREN. I do not want to interrupt the hearing.

Mrs. MORELLA. Fine. Thank you.

Dr. Lenfant, let us hear from you, please.

STATEMENT OF CLAUDE LENFANT, M.D., DIRECTOR NATIONAL HEART, LUNG, AND BLOOD INSTITUTE NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

Dr. LENFANT. Thank you very much, Madam Chairwoman.

As you pointed out in your opening remarks, we are not dealing with a simple issue. In fact, I would like to say at the outset that there is nothing simple with what we are talking about here today.

Before addressing the issue of measurements, I would like to underscore again the importance of the particular public that we are talking about here.

There are approximately 12 million Americans who have coronary heart disease. One of the most significant factors for the development and worsening of this condition is blood cholesterol.

Approximately 500,000 people from this country die each year from coronary heart disease. To put that in perspective, within the time of our discussion here today I would like to say that that amounts to one person every minute in the United States dies from coronary heart disease.

I should really also underscore that these are dramatic numbers. We in the United States have made tremendous progress. During the last 25 to 30 years, we have witnessed a decline in the death rates of coronary heart disease which has been quite remarkable, and in fact is the envy of most of the Western countries, not to say all the countries in the world.

We in the United States have approximately 1.2 million heart attacks occurring.

Let me address the issue of the measurement by saying that since 1970 the National Heart, Lung, and Blood Institute has been extraordinarily occupied with how blood cholesterol would be measured, and how precise and accurate this measurement would be.

That has led to many reports in cooperation with the Centers for Disease Control, which in fact has resulted in the development of a network to assure as accurate as possible measurements of blood cholesterol.

When the National Cholesterol Education Program was created ten years ago, actually, one of the first actions of the program was to standardize as much as possible the measurement of cholesterol, and to provide recommendations which hopefully would be followed by all the laboratories and measurement sites in the country.

At this very moment, we have some reports on the measurements and recommendations, I would say, on the recommendations of HDL, LDL, triglycerides, which are being completed and hopefully will continue to improve the measurements of blood cholesterol and its derivatives.

I should say very clearly here that the National Heart, Lung, and Blood Institute and the National Cholesterol Education Programs are in agreement with the GAO report. We do not dispute the fact that the system is not perfect and that much more work needs to be done to improve it.

However, I would like to say that perhaps the problems in the performance of the laboratories, as well as the implications of what they do, particularly relative to misclassifications, may be a little bit overstated.

In fact, the GAO report itself states that precision has improved quite markedly over the years and is now at an acceptable level.

My colleague here did mention the problem that we have in some measurements, particularly using standards, because of what is called a "matrix effect." That is indeed a very serious and considerable problem that needs to be addressed.

It is our expectation that these problems might be eliminated within some reasonable period of time in view of the fact that the Institute has initiated a research program to address this very issue and eliminate the problems.

The question—one of the questions that was raised in fact in your own introductory comments, Madam Chairwoman and Mr. Tanner as well, is the consequences of one determination.

I would like to submit that it is very unlikely that in this country today an interventional program, such as dietary intervention or drug intervention would be initiated on the basis of one single determination.

The National Cholesterol Education Program advocates and recommends the use of several measurements. It is our observation that even in general practitioners' offices, in most instances more than one measurement is being made.

Let me address the issue of misclassification which was mentioned. That is indeed a most important issue that we are talking about here.

It is absolutely correct that the classification for the categories of cholesterol levels are determined, classified in a very discrete fashion. In fact, to qualify the whole range of blood cholesterol levels that you see or can see in a human being that goes from say 160 milligram per person to as high as 700 milligrams and even higher, all that is categorized with three words, which are "desirable," which are "borderline," and which are "high cholesterol."

Those are the discrete classifications. But the fact of the matter is that the relationship between cholesterol and the risk—the risk—of coronary heart disease is continuous. What that leads you to is to recognize the fact that just one single number is not what is going to lead the physicians to install a regimen for the patient. Many other factors will be taken into consideration.

It is absolutely important to recognize that the Cholesterol Classification Guidelines, which are provided, are in no way a substitute for medical decision-making, and that the physician's clinical judgment must play a role. No individual is put under a treatment just on the basis of one number, whatever that number might be. Many other factors come into play.

Having said all that, I would like to repeat again that in a general way we do agree with the report of the GAO. There are many issues which are not resolved.

He did mention the issue of the desk-top analyzer. He did mention the home-testing kit which was approved by the FDA not too long ago. These are issues which need to be addressed and deserve much scrutiny, but to put it simply I would say that the system as it is now may not be perfect but it works.

You have to put it in the context of what it is used for. to address a major public problem, and the results, the bottom line, really has shown that what is being done works. It may not be as perfect as we would like it to be, but the results are very, very satisfactory.

For the sake of time, Madam Chairwoman, I would like to conclude my remarks here and I would be pleased to address questions.

Thank you, very much.

[The prepared statement of Dr. Lenfant follows:]

Statement by

Claude Lenfant, M.D.
Director

National Heart, Lung, and Blood Institute

National Institutes of Health

on

CHOLESTEROL MEASUREMENT,

CHOLESTEROL LOWERING,

AND

THE REDUCTION OF CORONARY HEART DISEASE RISK

Committee on Science

Subcommittee on Technology

United States House of Representatives

February 14, 1995

Thank you, Chairwoman Morella. It is a pleasure to be here today to discuss cholesterol measurement in the context of national efforts to reduce the burden of coronary heart disease (CHD). An estimated 12 million Americans have CHD. Despite 30 years of declining CHD death rates, it remains the leading cause of death for both women and men in the United States. This year, CHD will account for almost 500,000 deaths, divided about equally between women and men. CHD is also a leading cause of illness, producing about 1.25 million heart attacks a year. The annual economic cost of CHD is estimated at between $50 and $100 billion.

One important approach to reducing the burden of CHD is to control the risk factors that contribute to it. Modifiable CHD risk factors include high blood pressure, smoking, high blood cholesterol, obesity, and physical inactivity. In accordance with the Congressional mandate to ensure rapid dissemination of information about CHD prevention to professionals, patients, and the public, the National Heart, Lung, and Blood Institute (NHLBI) conducts and coordinates educational programs that address CHD risk factors. One of them, the National Cholesterol Education Program (NCEP), was started in 1985. The goal of this technology transfer program is to provide health professionals, their patients, and the public with the latest scientific knowledge so that they can make informed choices to reduce CHD risk.

Evidence from various lines of scientific inquiry, including animal, biochemical, genetic, metabolic, epidemiological, and clinical studies, shows that the higher the blood cholesterol level, the greater the CHD risk, and that lowering cholesterol levels reduces that risk. Through the NCEP, the NHLBI pursues two strategies for helping to reduce the prevalence of high blood cholesterol. One, the high-risk or clinical approach, fosters detection and clinical treatment, with diet alone or diet combined with drugs, of individuals whose high blood cholesterol and other risk factors place them at significantly increased CHD risk. The other is a public health approach to make the public aware that heart-healthy eating patterns can help lower average blood cholesterol levels and thereby reduce CHD rates. The NCEP Coordinating Committee comprises representatives of over 40 health-related organizations in the private and public sectors, including voluntary groups and State governments. It is the consensus of the Committee that the high-risk and public health strategies, which complement each other, should be used together to reduce CHD risk.

Ensuring Quality Cholesterol Measurement

The NHLBI commitment to accuracy and precision in cholesterol measurement began with its Lipid Research Clinics Program, which first demonstrated in the 1970s that it was possible to obtain precise and accurate cholesterol measurements. The Institute has continued to ensure careful standardization of cholesterol measurement in each of its many population-based studies and clinical trials. It has also assumed responsibility for, and supported, cholesterol measurements taken in the periodic National Health and Nutrition Examination Surveys (NHANES) conducted by the National Center for Health Statistics.

In 1971, the NHLBI began an Interagency Agreement with the Centers for Disease Control and Prevention (CDC) that has led to improved reference methods, materials, and procedures for cholesterol measurement in research laboratories. In addition, improved equipment for measurement has been developed by the clinical chemistry industry. As a result, the system now in use for ensuring the accuracy of cholesterol measurement is regarded as a model for analysis of other substances in tissues and blood.

Standardization of cholesterol measurement is a high priority of the NHLBI. When it established the NCEP, the NHLBI emphasized the importance of reliable lipid values; one of the first NCEP actions was to establish a Laboratory Standardization Panel. The panel developed two reports on total cholesterol. In addition, an advisory group of the NCEP recently prepared reports on LDL-cholesterol, HDL-cholesterol, and triglycerides. NCEP reports on the management of high blood cholesterol have not only stressed the importance of proper measurement but also considered measurement limitations in their recommendations.

The NHLBI is in general agreement with the thrust of the GAO report. In addition to reaffirming the need for accurate and precise measurement, the report identifies a major problem, namely the so-called "matrix effect," by which certain characteristics of the reference materials used in laboratories can interfere with the method for cholesterol measurement. Because of the matrix effect, current laboratory reference materials are not fully adequate for standardizing cholesterol measurements or for conducting proficiency testing.

However, the extent of the problem in actual laboratory performance may be overstated. Although comprehensive data on national laboratory performance are not available, the GAO report, itself, indicates that measurement precision gradually improved over the past few years and is now at an acceptable level. In addition, the original evidence of suboptimal performance was based on proficiency testing materials that were subject to matrix effects, and it has been shown that apparently poorly performing laboratories, when retested with fresh serum samples, meet standardization criteria. Further, when the current approach of "total error" is used as the criterion, to take into account both precision and accuracy, performance appears much improved. A collaborative study by the CDC and the College of American Pathologists to correct for matrix effects showed that, based on total error, over 90 percent of surveyed laboratories met the goals of the NCEP and of the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

As an important safeguard against inaccurate measurement and, also, as a measure to take into account normal biological fluctuation in individual cholesterol levels over quite short periods of time, the NCEP has consistently emphasized the need for multiple determinations. From 2 to 4 samples should be analyzed, especially when there is a considerable difference between the first two samples. In most cases this helps ensure sufficiently accurate values.

Moreover, the possibility of misclassification may be less serious than it appears at first sight. The relationship between cholesterol and CHD risk is continuous over the range of values encountered. Patients with cholesterol levels slightly above and slightly below values designated as separating risk categories have essentially the same CHD risk, and the physician's clinical judgment is needed to deal with the issue. This is similar to the situation with respect to blood pressure measurements; that is, categories of blood pressure levels serve as guides to physicians, but not as substitutes for medical decision-making.

Despite much attention and considerable progress, cholesterol measurement is not yet entirely satisfactory and will not be until a suitable reference material free of matrix effects is developed. However, the aforementioned evidence of improved laboratory performance and the impact of multiple measurements should help reassure Americans that their cholesterol test results are usually reliable.

The NHLBI shares the concern of the GAO report that measurement of cholesterol and related blood fats using desk-top analyzers may be unsatisfactory in many doctors' offices. However, the ability to measure a patient's cholesterol rapidly is of practical value, especially for the preliminary assessment. It is hoped that implementation of the CLIA requirements, including the proficiency testing and supervisory elements, will correct shortcomings in this area.

The recent advent of home cholesterol testing kits is an interesting development. At this stage they have undergone little evaluation in the field, and both their technical performance in actual use and their possible role in screening and monitoring patients are unclear.

To ensure further the quality of cholesterol measurement, the following steps have been taken. The National Reference Method Laboratory Network for Cholesterol Standardization has been established under the auspices of the NHLBI-CDC agreement. Its nine voluntary laboratories, widely distributed throughout the country, have each set up the reference method for cholesterol (the Abell-Kendall method) and offer evaluation of performance of laboratories using fresh blood samples, thus bypassing the matrix problem. Although only a small fraction of the nation's laboratories are likely to assess their performance in this manner, use of the network by industry is significant. As indicated in the GAO report, an estimated 95 percent of the different categories of instrument systems most commonly used by United States laboratories have been certified by the network as meeting NCEP standards. This should have a widespread, beneficial impact on the quality of measurement.

To assess an individual's CHD risk, it is often necessary to go beyond a total cholesterol measurement and determine the levels of HDL- and

LDL-cholesterol and triglycerides. To improve performance in these areas, the Working Group on Lipoprotein Measurement of the NCEP has recently completed three detailed reports that set out performance goals for each lipid component. The reports will appear shortly.

Finally, NHLBI recently solicited Small Business Innovation Research grant applications to develop methods and/or materials for accurate measurement of cholesterol (total, HDL, and LDL) in fresh human serum, with the elimination of matrix effects.

Importance of Lowering High Blood Cholesterol

Angiographic studies examining changes in the coronary arteries show that cholesterol lowering slows the progression of fatty deposits in the arterial wall and actually induces a reversal of some deposits.

Results of clinical trials with the statin class of drugs promise to be significant because the drugs produce greater reductions in LDL-cholesterol than other classes. An important trial, with a wide range of implications for people both with and without CHD, is the recently completed Scandinavian Simvastatin Survival Study (4S). In 4S, 4,400 men and women with CHD were treated for 5 years; half received simvastatin and half placebo. In the simvastatin-treated group, a 25 percent reduction in total cholesterol and a 35 percent reduction in LDL-cholesterol produced a 34 percent reduction in major CHD events, a 37 percent reduction in angioplasty and coronary bypass surgery, a 42 percent reduction in CHD deaths, and a 30 percent reduction in deaths from all causes. There was no increase in any noncardiovascular causes of death, including cancer and suicide, accidents, and homicide, despite the very large degree of cholesterol lowering that was achieved. Women and men showed the same degree of reduction in major CHD events. Reduction of CHD risk was seen in patients both above and below the age of 60, but the over-60 group had a larger absolute reduction in CHD deaths than the under-60 group. For patients with CHD, 4S confirms and extends the results of meta-analyses of other trials and shows that aggressive cholesterol lowering not only reduces illness and death from future CHD events, but actually prolongs life.

The 4S results also have implications for patients without CHD. They demonstrate that cholesterol lowering itself is safe and that a very large cholesterol reduction produces a correspondingly large reduction in CHD risk without increasing the risk for other illnesses and causes of death. Primary prevention trials (in patients without CHD) have not shown a decrease in total mortality, and 4S, with its large cholesterol reduction, is the first trial of any kind to do so definitively. Moreover, the absence of any increase in noncardiovascular causes of death tends to allay the concern that cholesterol lowering itself may somehow be harmful. The 4S, with its 5-year horizon, also provides a substantial measure of reassurance that use of statin drugs is unlikely to be hazardous, although longer experience will be needed to assess this issue fully.

The important evidence from 4S about the safety of lowering elevated cholesterol levels complements the growing view that low cholesterol levels themselves are not harmful. The apparent association between low cholesterol levels and noncardiovascular-disease deaths more likely reflects the fact that the disease itself is causing low cholesterol levels, or that another factor, such as high alcohol intake, has confounded the relationship.

The 4S also suggests that women and the elderly are as likely to benefit from cholesterol lowering as middle-aged men. Because the issue of cholesterol lowering in the elderly has recently been raised, a brief comment in this area seems appropriate. A recent small study observed persons 71-104 years old (mean age 79 years) for 4 years, and found no association between elevated cholesterol levels and increased risk for CHD. However, evidence from other observational studies indicates that cholesterol is a risk factor for CHD in the "young elderly," those less than 80 years of age. The number of CHD cases attributable to elevated cholesterol is actually higher at age 70 than at age 60. It is only for the "old elderly," those in their 80s, that doubts remain about the value of screening and treatment, especially with drugs. The limited findings of the new observational study, which had very few CHD events, are not a basis for altering current cholesterol recommendations for the elderly. In fact, the potential for reducing CHD in the elderly is quite high, especially when a patient's biological, rather than chronological, age and all other CHD risk factors are considered.

Aggressive cholesterol lowering in patients with CHD (i.e., "secondary prevention") is expected to have a large impact on overall CHD rates. Patients with existing CHD will account for about half the heart attacks in the next year. Reducing the rate of recurrent CHD events by 35-45 percent, as seen in 4S, would thus reduce overall CHD rates by about 20 percent. In addition, individuals who are treated will have substantially less illness and a prolonged survival.

Although secondary prevention efforts markedly reduce CHD risk in persons diagnosed with CHD, such persons nevertheless continue to have a much higher risk of future CHD events and death than the general population. Moreover, secondary prevention is of no value to persons whose first evidence of CHD is a fatal heart attack. Therefore, primary prevention of CHD, before it occurs, is vitally important. Atherosclerosis is a long-term process that does its damage over decades. Cholesterol and the other CHD risk factors have to be kept in check before CHD is evident. In general, a 1 percent reduction in cholesterol produces about a 2 percent reduction in CHD rates. The benefits of cholesterol lowering are likely to be significant in both human and economic terms.

Impact of Public and Professional Education

Evidence is growing that cholesterol education is having an impact. Surveys of physicians and the public show that attitudes, knowledge, and practices related to cholesterol improved substantially during the 1980s. For example, the percentage of the public who reported ever having blood cholesterol checked rose from 35 percent in 1983 to 65 percent in 1990. Between 1978 and 1990, Americans reduced their total fat intake from 36 percent of calories to 34 percent, and their saturated fat intake from 13 percent of calories to 12 percent. In the same time period, average total cholesterol declined from 213 mg/dL to 205 mg/dL; the percent of adults with high total cholesterol levels (240 mg/dL or above) dropped from 26 percent to 20 percent; the percent with desirable cholesterol levels (less than 200 mg/dL) rose from 44 percent to 49 percent; and the percent with blood cholesterol levels requiring dietary therapy declined from 36 percent to 29 percent. These results reflect a downward shift of cholesterol levels across the entire range of levels and an acceleration of a decline that dates back 30 years. Finally, CHD death rates have continued to decline, and in 1993 were more than 50 percent lower than in the 1960s.

Effective prevention has played a significant role in the progress made against CHD. We believe declines in cholesterol levels reflect the 30-year trend in improved eating habits by the United States public. A heart-healthy eating pattern has a wide range of benefits beyond its effect in lowering LDL-cholesterol. For example, it helps control weight, which in turn enhances blood pressure control, raises HDL-cholesterol, and improves control of blood sugar. A lower intake of saturated fat may reduce the risk for clotting in the coronary arteries, and higher intakes of fruits, vegetables, grain products, and fish may help protect against CHD. For these reasons, diet is the mainstay of both the high-risk and the population strategies of the NCEP.

Choice of Treatment and Cost Considerations

Based on the updated Adult Treatment Panel II (ATP II) dietary recommendations issued in 1993, it has been estimated that dietary therapy, together with weight control and physical activity, may be expected to produce an average 10 percent reduction in LDL-cholesterol levels. In secondary prevention, diet remains important, but drug treatment becomes appropriate in a larger proportion of patients, given their high risk for a future CHD event. Overall, it is estimated that three-fourths of all patients who need cholesterol-lowering intervention will require only dietary therapy, and one-fourth may need the addition of drug treatment. Currently, approximately 5 million individuals are taking cholesterol-lowering medication, which is substantially fewer than the number for whom drug treatment is warranted by the ATP II guidelines. Thus, data suggest that a vast overuse of cholesterol lowering medications has not occurred.

To gauge the economic aspect of cholesterol lowering, cost-effectiveness analyses have been performed, most of which have focused on drug treatment. An NHLBI conference on cost-effectiveness of cholesterol lowering reviewed findings of a variety of cholesterol studies. They showed that the public health approach is highly cost-effective. In clinical treatment, three categories of patients can be identified:

1. For patients with CHD, cholesterol lowering with drugs is not only cost-effective but is actually cost-saving, i.e., it is cheaper to lower cholesterol than not to do so, because of the costs avoided for expensive treatment of averted CHD events.
2. For patients with multiple risk factors and high cholesterol levels, cholesterol lowering with drugs is cost-effective.
3. For patients with high cholesterol as their only CHD risk factor, cholesterol lowering with drugs is often not cost-effective.

These categories, based on cost-effectiveness, parallel the categories of patients for whom the ATP II guidelines recommend drug treatment based on risk-benefit considerations. For patients with sufficiently high CHD risk, the benefits of using cholesterol-lowering drugs both outweigh the risks and justify the cost. In patients whose CHD risk is not high, the potential adverse effects of drug treatment may outweigh the benefits, and the costs are not warranted. For selecting appropriate high-risk candidates for drug treatment, the ATP II recommendations provide appropriate guidance to health professionals.

Conclusions

In summary, it is advisable to continue to do two things simultaneously:

1. Provide information about cholesterol to professionals, patients, and the public that enables them to make informed and sound choices and encourage them to use it.
2. Encourage continued improvement in cholesterol measurement performance, especially with respect to HDL, triglycerides, and LDL.

I believe that the evidence I have provided to you demonstrates the effectiveness of these approaches. I would be pleased to answer any questions you may have.

Mrs. MORELLA. Thank you, Dr. Lenfant. We appreciate your testimony with regard to the work that is being done at the National Institute, and also explaining what NCEP has done.

You know, I have this feeling that what you have been doing is telling people that they should "know their number"—and I have heard this on commercials; know what your number is—and yet, one of the problems is that there is no special number. It is really a range, and it is a range that can vary. It can vary according to whether we have the trauma of voting on a crime bill, or trying to make three committee meetings at the same time and realizing we are going to be late for one, and maybe not even make another one, and that that will have a major effect.

I wondered if you think that maybe we should change that slogan of "know your number" to "know your range"? If you would like to comment on that, I would like to hear your response.

Dr. LENFANT. Well I think the points that you are making are extremely important. That is what indeed is being followed in triggering the decision for a treatment or not.

However, if you want to alert the public of something which is important, we know from many, many situations in public health, or whatever, that the public would become very quickly confused, if I may say that, if we gave lots of information at the same time.

We know that this slogan, "know your cholesterol" has been extraordinarily successful in raising the awareness of the public about the relationship between cholesterol and coronary heart disease, in modifying by themself their dietary habits, their lifestyles, exercise, and what have you.

It plays a role a little bit like a, if you want, like a beacon. It is something that you see, you hear it, and you pay attention to it.

If you give a great number of things at the same time, people are confused and do not pay as much attention. You know, Madam Chairwoman, that we have a comparable program with high blood pressure, which has been extraordinarily successful, as well.

Here is the same thing. We have to give one number of what the blood pressure is and what should get you to do something about it. That does not mean that something is going to be done because that number is going to be assessed, but it is getting the person, the public to do something about it.

Mrs. MORELLA. You know, your premise though almost seems to be that you have to make it so simple so the public will understand it.

Dr. LENFANT. Yes.

Mrs. MORELLA. And I would submit that the public care about their health. I mean, they are checking fat grams, and they are reading labels now that we have all the nutritional ingredients on it, and they are getting cholesterol tests and measurements.

I would submit that what you are saying is kind of demeaning their intelligence. You are saying they can only go for a number, whereas it seems to me it is simple enough to know that a range would be appropriate.

For instance, you can see three different areas here. The desirable, you know, up to 200; the borderline high with a radius of 200 to 239; and high, which would be the dangerous, 240 and above.

It seems to me that we need to be more accurate in saying to the public "know a range" instead of a number.

Did you want to comment on that? I will yield to the gentlelady from Texas.

Ms. JOHNSON. Thank you.

You know, in looking through the report and from some experience, the way the blood is drawn has a lot to do with the result.

Dr. LENFANT. Yes.

Ms. JOHNSON. Many of the tests that people can perform on themselves will not be perhaps as accurate as blood drawn from the—venous blood.

Dr. LENFANT. Yes.

Ms. JOHNSON. That makes it a little difficult for someone to do an accurate test on themselves in the self-help type kits. But the range also depends a great deal on history, that person's individual genetic history, as to what a physician would look at a profile of that patient and then give them some warnings, and how stable that level is.

So it is more complex than a simplicity type of approach to it to keep some kind of real attention on where your health status might be as it relates to the amount of oil, fat, in your blood stream.

And as this oil accumulates, it eventually attaches itself to that inside of that vein, and then you start to get sclerosis. So I do not believe it is going to be real simplistic soon in how we can just kind of turn it over and say, you do your own; if it is in this range, you come; if it is not, you do not have to come see about it. Could you comment on that?

Dr. LENFANT. Well, it is correct that the slogan that we use is "know your cholesterol," but the presentation, if you want, of this number is always to say: if it is below 200 milligrams, that is normal. That is where we would like to see you.

If you are between 200 and 240, you are borderline. That number is always placed within a range of what would be a level, if you want, of health status.

And we say, as well, if it is above 240, then you really have to do something about it.

And what you say, Mrs. Johnson, is absolutely correct. There are lots of elements which are going to influence the findings. That is one of the reasons, in fact, when a measurement has been made that it is important to repeat it in order to confirm or negate whatever the first finding has been.

Mrs. MORELLA. Thank you.

I am going to reclaim my time. I am going to give us all a five-minute rule for the first round, if that is okay, so we can get around to everybody in asking questions.

So you would agree, then, it is "know your range," since you just reiterated that—

Dr. LENFANT. Yes.

Mrs. MORELLA. And maybe we will need to change this kind of motto to something more accurate.

You also talked about a mention had been made of the desk- top measuring devices; that there is a—I would consider it, and I guess you would agree—an inaccuracy rate of I think I jotted down 17 to 50 percent of patient samples might well be misclassified?

Do you think that is acceptable?

Does that say there should be standards on these measurement devices?

Dr. LENFANT. The report of the GAO—and Mr. Chan can confirm that—does state that at this point in time the approximately 90 to 95 percent of the measurements are within the norms which are recommended by the National Cholesterol Education Program.

The example that he gave of a 16 to 17 percent error is on the one measurement. Our perceptions, although admittedly these data are extraordinarily difficult to find because there are so many physicians, or centers, or what have you, making these measurements, that most of the measurements are not simple ones but in effect repeated measurements from which an average is drawn.

Mrs. MORELLA. Did you want to comment, Mr. Chan, on that?

Mr. CHAN. Well, I think what we are trying to present is basically, if you look at it broadly with all these different types of analyzers, there are some that are highly accurate in terms of getting the reference standards, and they are in fact checked out that way, and there are different types and there is a broad range of accuracy one can produce.

So I think it is sort of important to recognize that as a, you know, a fact first so that one can in fact then begin to reach what Dr. Lenfant is trying to say, to get some reference standards by which one can do the checking.

I think the industry, as we say, is generally very good. There you have, you know, variations within that. The question is, how do you approach this problem?

Mrs. MORELLA. Evidently there are tremendous variations.

Mr. CHAN. Yes.

Mrs. MORELLA. It is wonderful that we have both of you together because you can get a kind of a response. Someone can make a comment, and someone can respond to it, too.

I wanted to turn now to Congresswoman Cubin because she is going to have to leave, before I go to the Chairman of the Committee and the Ranking Member of the Subcommittee.

Mrs. CUBIN. Thank you, Madam Chairman, for letting me ask my questions out of order.

I know that research on women in practically all the medical fields has been slow in coming. So what I want to know is, are you satisfied that the results that you have on cholesterol for women are as good as they are for men?

I know even breast cancer—I was told even breast cancer research was done originally on men. I also know that a lot of women die of heart attacks because they are not aware that the symptoms that they have are those of a heart attack because they are different than in men.

Are you satisfied that this is accurate enough, that enough studies have been done on women that women and men should be classified together in this study?

Dr. LENFANT. Yes. There are no known reasons to assume or say that the cholesterol measurement would differ between men and women, the technique of doing it.

Mrs. CUBIN. Right.

Dr. LENFANT. There are some different biological factors between men and women, but I can tell you that a blood cholesterol measured in a woman or in a man would be leading to just as good a decision depending on what your number is of the cholesterol level.

In fact, you may recall that the Chairwoman indicated that she met with me yesterday. She met with me yesterday because we were telling her about the study and the effect of hormonal replacement therapy in post-menopausal women and the impact of that on the risk factor of coronary heart disease.

That is not the purpose of these hearings, but it is such a wonderful study that I felt compelled to mention that to you.

Mrs. CUBIN. Thank you.

Thank you, Madam Chairman.

Mr. CHAN. Can I answer that? I think I would like to answer it a little differently.

One is that I think the question implies whether there are enough scientific data about women, and I think our second study will address that in terms of clinical trials, in terms of what population is being tested over the past 20, 30 years. That may be helpful to understand.

The second thing I think is sort of important is that what Dr. Lenfant said is true, that the measurement itself should not be different. But I would suggest that, based on the studies we review, that the biological variation for women may be somewhat different and, with that variation, the interpretation information might be different.

One, as I mentioned, is issues such as pregnancy. That changes the cholesterol, of what you actually have versus what you are eating; menopause; oral contraceptives, use of that; as well as, you know, the general issue about women, the way they exercise or not, and so on.

The other thing I would like to show that is sort of an interesting one is, if you have the report on page 21, we actually try to make some comparisons between men and women, particularly in terms of their cholesterol as a population versus age.

[Pause.]

So what you can see in here is, up to 45 to 54, the total cholesterol, the crossover sort of begins as women exceed that of men, for example. Whereas, if you look at the LDL, which is often the so-called “final gate” to determine whether any kind of interventions occur, the women’s side is much lower as a population and the HDL is higher, which is really the beginning of the measurement that is becoming much more important as the science moves on.

Mrs. CUBIN. Thank you, very much.

Mrs. MORELLA. Very interesting.

Thank you, Mr. Chan.

I wanted to introduce and to acknowledge the fact that the Chairman of the Full Science Committee is here, Bob Walker from Pennsylvania. Chairman Walker is Ex Officio on all of the subcommittees and chose to come by for this important hearing.

Chairman WALKER. May I ask some questions?

Mrs. MORELLA. Indeed.

Chairman WALKER. Thank you, Madam Chairwoman.

I think it is important to recognize that these hearings are looking at an issue that has macroeconomic impact well beyond the narrowness of the science. I think that is the reason why we are here.

There is an awful lot of money invested in keeping cholesterol as a key risk factor in health decisions. I think that is one of the questions that we are going to have to answer along the way.

Let me ask the GAO. Have you begun to investigate the efficacy of cholesterol as a key component in heart disease?

Mr. CHAN. We have basically our second study, as Madam Chairwoman mentioned in her statement, to look into the clinical trials and the scientific foundation by which this National Cholesterol Education Policy is based on.

So in that sense, we are looking for the evidence to support that.

The final study will be to look at, based on the policy and guideline, what impact has it had in terms of our medical health as well as the food industry. That gets into the macro issue that you are talking about, and we have not reached that stage yet, sir.

Chairman WALKER. Is it fair to say that there is now a variety of science out there indicating a variety of conclusions, depending on who is doing the research?

Dr. LENFANT. Well if I may address that, Mr. Walker, I don't know for sure what you mean by "a variety." If you mean as much going one way as as much going the other way—

Chairman WALKER. Is this an issue in dispute?

Dr. LENFANT. In my views, no. There is a small minority of persons who will argue about what I think are small points. primary prevention versus secondary prevention. Primary prevention would be to prevent a condition to happen. In the case of what we are talking about, what can we do to prevent you or me from having a heart attack?

Secondary prevention is that you and me have had one and we want to prevent a second one from occurring. So there are some variations with regard to that.

Chairman WALKER. So the article in Atlantic Monthly called "The Cholesterol Myth" is in fact representative of only a small group of science researchers in the country? This does not represent a growing—

Dr. LENFANT. Yes, and that is almost ancient history. I was very much involved with that. I am sure that my name must be floating around in this article. That was several years ago.

I think that Mr. Moore, the author of this article, today would have no basis whatsoever to advance what he said in this article. In fact, just a few months ago a study was reported that negates in a very forceful way all the allegations and attributions which were in this article.

Chairman WALKER. So this article written in September 1989 is no longer valid, in your opinion?

Dr. LENFANT. Absolutely. And that is not a scientific article, Mr. Walker. It is for the public, and it is no longer sustainable.

Chairman WALKER. It is no longer valid.

My experience in 18 years of watching science policy being made is it is often those small groups of scientists, though, who differ with conventional wisdom that in fact are producing the scientific judgments of the future—not always, but they are not always wrong. They just defy conventional wisdom.

Do we have some assurance that these people are simply horribly, terribly wrong and do not represent reality in terms of where the research may take us in the future?

Dr. LENFANT. My answer to that would be, yes.

Chairman WALKER. And you know of no scientific groups at the present time who are kind of pressuring these people, trying to squelch the research that is going on that is being done that presents an alternative point of view?

Dr. LENFANT. I am not aware of that at all.

Chairman WALKER. Has GAO—

Dr. LENFANT. In fact, if I was aware of that, I would object to it. Because I think scientific knowledge acquisition has got to be coupled with integrity and looking at all the points of view.

Chairman WALKER. Has GAO felt any pressure as you have engaged in these areas from people who are raising questions about the direction that your studies are going?

Mr. CHAN. Let me answer in a different way here [laughing].

Chairman WALKER. I would prefer to have it answered the way I asked it, but—

[Laughter.]

Mr. CHAN. I think we have—let me say, Mr. Walker, we have sought out other dissenting voices to see what views they have, and to see to what degree scientific efforts have been made. Okay? That we have done.

We are really, I think from a scientific point of view, we could not really evaluate whether these are sound science or not, as Dr. Lenfant has stated. But let me say that from our perspective—

Chairman WALKER. That is obviously not your—well, maybe I ought to—have you found evidences of the kinds of pressures I am talking about?

We are talking big bucks in this area, and we are talking about a lot of investments in all kinds of industries across the country. Is that coming into play as we look into this subject area?

Mr. CHAN. I think in my own mind I, as I say, I would like to answer the question in a different way. One is, as we've gone through the risk factor, my question is, why cholesterol and not something else?

So if the question you are posing is that—

Chairman WALKER. And in your mind that is a legitimate question at this phase of your research?

Mr. CHAN. It believe, you know, it came into my head when you asked had I thought about it, because there are other factors that, you know, are also—as you try to prioritize them, you see where the research is going.

Chairman WALKER. So in other words, at the present time one of your questions is not whether or not cholesterol may represent a partial risk, but it may not be the only risk, or it may not be the main risk, is what you are now saying; that there may be other risk factors that also need to be taken into account and may ultimately weigh just as heavily as cholesterol?

Mr. CHAN. From a cost/benefit point of view, that is the question you are posing that, you know, if we do this for—for example, hypertension clearly has shown itself to be very effective as an educational program.

There are other programs. The question becomes, what about the others? And how do you compare them if you want to determine where the research should go. Yes, I think it is an interesting question.

Ms. JOHNSON. Could the gentleman yield for just a moment?

Chairman WALKER. Sure. I would be happy to yield to the gentlelady.

Ms. JOHNSON. Regardless of the effectiveness of the test, if you determine what is accurate and what is not accurate, I think that there still might be some discussion as to whether or not cholesterol is important, and there has been a great deal of investment.

But on the test, is it possible, or is it recommended, or do you not recommend that perhaps some correction could be made as to warnings to persons who are using it, indicating that they might look for a different range with certain kinds of tests, does not make the tests completely out of use?

Mr. CHAN. No.

Ms. JOHNSON. But perhaps new instructions that would give warning about the type of test would look for certain kinds of ranges.

Would that be useful?

Mr. OPPENHEIM. It was never our intent with this study on measurement to question whether cholesterol was important to look at. I think, you know, we would agree that it clearly is.

Coronary heart disease is a multi-factorial, complex process and there are several risk factors involved. As we stated earlier, cholesterol is a key risk factor within that group.

I think in terms of the measurement issue, one of the gaps that is out there at the present is we do not have a good sense of what accuracy looks like in many of the field settings, so to speak, where cholesterol testing is actually done.

There is a fairly good set of research studies that shows accuracy can be achieved under fairly controlled conditions, but it is this other set of settings for which we do not have good information.

And providing more information to physicians and, I think, to the general public about the strengths and limitations of measurement and what variability is associated, might be something useful.

Chairman WALKER. I have taken my time here, but I just wanted to come back to the point that I thought we were getting to.

This committee's interest, among other things, is to make certain that public policy is driven by good science. Now I think what I hear you saying is that good science would indicate that cholesterol is a factor in heart disease and other health problems, but that good science may also indicate that it is not the only factor in those areas.

So therefore it ought to be weighed against other kinds of factors that it may produce. I think that is important for us as we begin to understand risk factors in overall public policy science judgments.

Is that an accurate reflection of what you were saying to me, Mr. Chan?

Mr. CHAN. Yes, sir.

Dr. LENFANT. Mr. Walker, I truly endorse what you are saying. It is absolutely correct that as a physician I could not conceive that, except for very special cases where you deal with what is called the "familial hypercholesterolemia" where it jumps at you because you have an enormously high level of blood cholesterol.

But for most cases, no judgment would be made just on the basis of cholesterol. The physician would look at other risk factors and makes a decision looking at the entirety of the situation and of the patients.

But blood pressure, weight, activity, mental states in terms of let's say Type A or Type B or what have you, and cholesterol are all elements; family history, which comes into the decision.

Chairman WALKER. Well, and I do not doubt that whatsoever. But I will tell you that there are other judgments being made out there that are not physician-based judgments.

I believe you are absolutely right if you have a physician involved, but there are a whole range of judgments being made by advertisers, by people making their own judgment about what they are going to do with regard to their own health, the foods that they buy. There are a whole set of macroeconomic judgments that do not necessarily involve a physician.

The fact is that in that whole decision-making process as it relates to public policy, much of that has been centered on cholesterol. I think our work here is to make certain that that rather enormous rating that cholesterol has gotten in terms of public judgment, both policy and individual, is in fact the right mix for the public to be focused on.

If there are a variety of factors the public ought to be focused on and that we as decision-makers ought to be focused on, then that ought to enter into our judgment, too, not just the judgment the physician makes once somebody walks into the physician's office.

Dr. LENFANT. You are absolutely correct with that, too, Mr. Walker. When the National Cholesterol Education Program began 10 years ago within the subsequent years we saw a great number of health messages, almost a prescription, appear on food product labels. They were all saying, "as recommended by the National Cholesterol Education Program," which was not correct. But that has stopped.

The Food and Drug Administration made its—developed its regulations regarding to labeling, and to my knowledge today that does not exist anymore.

Chairman WALKER. Thank you.

Thank you, Madam Chairman, I appreciate the time.

Mrs. MORELLA. Thank you.

We are going to be leaving to vote, but I cannot go off to vote without acknowledging that our Ranking Member, Mr. Tanner, has been very patient. Is it okay to wait for you to come back for questions?

Mr. TANNER. Yes, thank you.

Mrs. MORELLA. We will be back in about ten minutes.

Thank you.

[Recess.]

Mrs. MORELLA. Thank you. We will reconvene the hearing now.

I know that our Ranking Member has a number of questions and he has been very, very patient about waiting to be able to ask them, and I appreciate the courtesy he extended to the Chairman of the Committee. Thank you. I will turn it over to Mr. Tanner.

Mr. TANNER. Thank you very much. It is my pleasure.

This has been a good hearing. I am particularly interested in pursuing the education aspects of the hearing, as I mentioned in my opening statement. There seems to be some confusion perhaps in the marketplace about just how important a cholesterol number may be, based on what I heard.

It was interesting to note that in the GAO report there really were not any conclusions or recommendations drawn. If we look at this hearing today as an educational opportunity for the American people, it seems to me that we come down from the GAO report to the conclusion that:

One, one's level of cholesterol depends on many factors. One, the kind of equipment used and whether or not it is—how accurate it may be. Number two, the technique involved in drawing the sample for measurement. And number three, a whole range of other things, including activity, diet in recent days or weeks, and so on.

Is that a correct statement from your report?

Mr. CHAN. Yes.

Mr. TANNER. So we need, the American people need to know that a number on a given day may or may not indicate the need for follow-up or for further testing?

Is that—"a" given number of "a" given day?

[Pause.]

How important is—let me ask it another way. How important is a number from one test on a given day?

Mr. CHAN. Well I think it should be the beginning of understanding where you stand. I think it's—what we emphasize in our report is that even if there is a range that has certain cutoff points where a decision needs to be made as you move to the next step, and if someone is really at the extreme level such as let's say 350 milligrams or something, I think the likelihood that you need to pursue that is very strong; whereas, if you are very low, then you may follow the guideline and say, you know—and if the HDL is above 35 milligrams, then you say, well, you should do testing once every five years as the program suggested.

But it is for the in between where we have issues on what you need to do in terms of variability because, you know, the other are much easier to make decisions on, even if there is 16 percent variability to those low or high numbers.

You know, you are still fine if you are below that. You are not fine if you are above that.

Mr. TANNER. In your report you stated that in 1990 65 percent or so of the public reported that they had had their cholesterol checked. Do we have any data as to where this occurs? In a doctor's office? At a health fair? At a rolling clinic?

And if we know, given the variances— what I am after here is the difficulty we have in pinning down accurate information from a reading of your report, and how inherent in all of these things the opportunity for fairly major variances exist.

Mr. OPPENHEIM. I think we don't have information what type of settings those tests were done in. We do know there is a fairly large number of labs in this country, some 150,000 different labs, that have registered with HHS under the Clinical Laboratory Improvements Act of 1988.

Of those 150,000, those cover everything from clinical labs, to physician office labs, to public health screening type settings. So we know that there is a diverse range of settings. We know there is a diverse range of devices that are used on the market end.

Mr. CHAN. NHLBI Cholesterol Awareness Survey—they have done three of them since 1983, in '83, '86, and 1990—over this period, at least the way we understand the data from the survey, it is that they have gone from 79 percent physician doing testing for their patients to 95 percent the physician are doing testing on their patients. So there is a marked increase over that period. That may contribute to somewhat, not the entire thing, but to the 65 percent you are talking about.

Mr. TANNER. Insofar as we have seen a proliferation in the market of the home testing and the desk-top testing and so forth, may I ask are there standards for the manufacture of those types of devices to ensure that, as best we can, they are calibrated to be as accurate as they can be under any reasonable circumstances.

Dr. LENFANT. Yes, Mr. Tanner. The National Cholesterol Education Program and the Institute has an agreement with the Center for Disease Control from which has been created something which has been called the "National Reference Method Laboratory Network for Cholesterol Standardization." It is kind of a mouthful, but the fact is that it is a very important concept which leads to the, if you want, approval of the methodology used and the various instruments used by this organization using a common set of standards.

At this point in time, 95 percent—95 percent—of the categories of instrument systems most commonly used in this country have been certified by the Network as meeting the standard of the National Cholesterol Education Program.

Mr. TANNER. Are you satisfied with that Standard?

You said in your testimony that there were some shortcomings in our present system, but that they could be fixed. I understand that there were—the NCEP expects to issue some new cholesterol measurement guidelines regarding the HDL and LDL in the future.

Are you satisfied that the equipment out there now that meets this 95 percent, as well as these Guidelines that will be coming out, will correct the shortcomings you referred to?

Dr. LENFANT. I am satisfied that what is being done is indeed going to lead to much, much, much better results. The equipment is, as far as I can tell from this standardization procedure and approval processes is satisfactory. Its guidelines which are going to be issued is what you do once you have the equipment, how you use it and so forth. That is certainly going to improve the process.

Also, earlier Mr. Chan and myself have spoken about a very major problem regarding the standards which are used to test equipment where there is a problem. We are now working—we have initiated a research program in order to eliminate these problems.

Once all that will be done, if there is another hearing, I can assure you that we will give you, and I am sure that the GAO will agree with me, we will give you much, much better results—much, much better results.

The thing that we may not have mentioned is that in about 30 years ago there was a recognized error of approximately 24, 25 percent in all these measurements. Today it has been reduced to approximately 9 percent.

It is progress. It is not perfect. But I think that the government, industry, the Department of Health, the Congress when it created the Clinical Laboratory Improvement Act, working all together are putting into place the process needed to improve that situation.

Mr. CHAN. If I may answer from more of a process point of view, I believe that the home units was approved by FDA through the 5.10K process, which means that it is essentially equivalent to whatever is existing out there.

It does not require that device meet that standard that Dr. Lenfant talked about.

Mr. TANNER. Do you view that as a major shortcoming in the system?

Mr. CHAN. I don't know. I think at the moment—

Mr. TANNER. I am not trying to put words in your mouth, but the bottom line is to try to alert people who are using these things when they have a problem so they will seek further treatment, and to not give false readings to those who do not have a problem.

The more accuracy we can bring to the entire scope of the delivery system, it seems to me, the better the American people, the better opportunity they have to take care of their health by using these devices.

My question goes to the standards that they have to meet to go on the market so people can have some faith, or they have some credibility in terms of testing.

Mr. CHAN. Go ahead.

Mr. OPPENHEIM. I think the process that was set up really was to provide resources so labs and manufacturers could assess the accuracy of their equipment. It was not necessarily to require that everybody use the same equipment, and that everybody have the same method for testing cholesterol.

I think the resources are out there for labs to utilize if they want to assess accuracy, and there are a number of testing programs out there, proficiency testing programs. There is a CDC network of labs where they can assess the reference method. CDC provides these reference materials to commercial labs and other labs around the country.

There are a couple of states that also have programs, and a private group such as the College of American Pathologists which run testing programs.

These facilities and resources are available to labs to participate in. One possible drawback to that has been participation by labs in these programs which to date has been somewhat small, I would say, and probably even smaller among physician office labs where a lot of routine testing is done.

Another piece of the picture is the Clinical Laboratory Improvement Act, which is going to now require quality control procedures in labs, and also set up requirements for those labs to participate in proficiency testing programs.

So because of that, there should be even further information coming down the road on testing by these programs.

Mr. TANNER. One follow-up, and I know I am running over my time, Madam Chair. It is our information that only 167 or so labs out of 150,000 are participating, though.

Mr. OPPENHEIM. In the CDC Reference Study.

In the CAP Program, the College of American Pathologists, there are something like 12,000 subscribers. I don't have the number for what the participation is in some of the other programs.

Mr. TANNER. I know I have overrun my time. Thank you.

Mrs. MORELLA. No, no. You were very patient to wait, and those were very good questions with regard to the accuracy of the testing devices. I have always wondered, myself, about the desk-top ones in terms of how one follows through with the kind of home testing kits they have.

But I wanted to now recognize Ms. Lofgren from California who has been very patient for questions.

Ms. LOFGREN. Thank you so much, Madam Chairwoman.

I am obviously new to this panel and new to this report, so I just have some very brief questions.

If I understand it correctly, we are really on a track to make sure that testing in laboratory settings is going to meet standards that physicians and their patients can rely on. We may not have it yet, but we have got a strategy that in all likelihood will achieve that result for our country.

Of greater concern to me is the desk-top results, as well as the home testing results. I have been thinking about it.

I heard the Chairman's discussions about whether cholesterol is or is not a cause of heart disease, and is it one of many factors, and that is certainly one analysis to go into, probably not as much by Congress Members but as physicians and researchers.

However, I am thinking of it from this point of view in terms of consumer protection. If I am reading this correctly, we have got people—home health providers and physicians—buying desk-top devices that essentially don't work, and in large amounts of the time.

One of these has a 36.8 percent false-negative rate, looking on page 48; and a 47.5 percent, if I am hearing this false-negative for venous blood; and I am concerned that, to the extent that physicians or home health providers, or health care promoters are buying these things, they ought to know what the level of accuracy is at a minimum, as well as for the home tests.

I really believe that people ought to have the right to control their own health. I am very keen on home testing kits. I am for that. But people ought to know how accurate it is, so that if it is 50 percent accurate they may not want to spend the money to buy it. They may rather take the money and go down and get a more reliable test.

So I am wondering what efforts our government is making to let physicians and consumers know that they may be spending good money for something that is not worth it. Is the CDC notifying physicians, or medical societies around the country?

Are we asking that information on accuracy be provided in drug stores across America?

What are we doing to advise consumers?

Mr. OPPENHEIM. Well I think if a consumer wants to know whether their physician is using a laboratory that is essentially using a machine that is accurate, I don't think they have access to that information. I can't really say if physicians have access to that, either.

My sense is that there are some studies going on now which are beginning to look at how the Guidelines are being implemented in physician-care settings. There is some evaluation work going on at the NCEP and the other education programs at the Institute.

But in terms of kind of the consumer awareness side, I don't think there are many mechanisms in place to get access to information on the labs and the accuracy of the testing within the labs.

Ms. LOFGREN. Well if I can just follow up, taking a look on page 48 of the report, the Liposcan, I don't know really anything about these machines, but it has a very high false-negative rating.

That I assume would be a concern. I mean, most Americans are not going to suffer if they stop eating fat. But if people feel that they are okay, then they will fail to take steps that they might need to take to protect themselves.

I would assume that a physician who has one of these machines would want to know it if they care about maintenance of their patients' health outcome.

It seems to me that we ought to, at a minimum, let people know, let physicians know these results so they can take prudent steps to avoid malpractice. I mean, are we going to do anything like that?

Mr. CHAN. I think I would agree with you. I think our study basically brings out what kind of research and surveys have been done so far. I think what it really needs to do is to do it much more broadly to see how it is practiced and used.

Ms. LOFGREN. So really my question ought to be directed to the CDC and not to you? Is that what you are very kindly saying?

Dr. LENFANT. May I comment on that? When I saw these data I was shocked to see them. These indeed are rather astonishing figures that we've seen here.

However, what we don't know—and I don't know that we have the ability to get this information—are two things. How many of these things, this Liposcan device, are used; and second, how many people go to offices where these devices are used?

So that makes it very difficult to get reliable information; but that does not change the fact that somebody should ask how come we have that piece of equipment which is so unreliable.

Ms. LOFGREN. The other question—and I know I am probably using up all my time already—but on page 48 it talks about the home test devices. I found this little chart on page—no 49 is the home test—very helpful to kind of understand what the variations are.

Do you have the data on the various kinds of kits available and what the variations are among them for the home test devices, as you do, and if so could I obtain that?

Mr. OPPENHEIM. There is really only one—

Ms. LOFGREN. There is really only one out there?

Mr. OPPENHEIM. It is called the "AccuMeter." I think part of the issue with it is some controversy really on how it is used.

I think according to the NCEP Guidelines, it is very strongly emphasized that patients ought to interact with their physician on assessment risk. I think the home test kit, although it certainly has convenience factors and possibly some cost efficiencies involved, the concern is whether or not it doesn't bring the patient in to interact with their physician for that full risk assessment, and not just cholesterol but other risk factors.

Ms. LOFGREN. Thank you, very much.

Mrs. MORELLA. Thank you, Ms. Lofgren. We are going to have two more hearings ultimately on the same subject, so we will get into more specific recommendations in terms of the clinical trials and the impact on the food industry, and medical health.

I am curious. Since I am one of many people who has this cookbook—I don't cook; my husband does—but it is on cholesterol-free cooking and is very popular. I am just wondering about how much reduction in cholesterol can be expected from a diet that is supposed to be a cholesterol-lowering diet?

I noticed, I think, NIH, according to a figure that I have seen, says that it is a 5 to 7 percent reduction? How do you measure it? Can it be measured? Perhaps I will ask Dr. Lenfant, and then ask you, Mr. Chan.

Dr. LENFANT. Yes, it can be measured. Lots of these patients who were found to have a high cholesterol were put on a dietary regimen to lower it.

If you take a set of cholesterol measurements at the beginning, and if you prescribe dietary changes, and you measure that six months later and you find very significant changes.

I know of people who can lower their cholesterol by 40 milligrams per 100 deciliters over six months just by following a diet. The dietary intervention is a very powerful intervention. The problem is to have compliance with it. That is the issue.

Mrs. MORELLA. I could not agree more on the difficulty with maintaining compliance—exactly, particularly as you run back and forth with those potato chips and all.

[Laughter.]

Mrs. MORELLA. But I also wondered if maybe a trip to Hawaii or something might have the same effect? I mean, how do you measure whether it is an environmental kind of thing versus a dietary thing? Just whatever happens to be in one's life?

Dr. LENFANT. We are really talking—what I think you are asking, perhaps indirectly, is what happened from migrants from say Japan to Hawaii to this country.

I can tell you, they are getting worse. In Japan they are much—doing much better than they do in Hawaii; and when they are in Hawaii, they do much better than when they are in California, for example.

That is a fact. But here what you are talking is the local dietary habits and what the population in general would eat.

But with regard to individuals, it does not matter whether you are in Japan, in Hawaii, or in California, or in Washington, if you follow a diet which controls cholesterol, that is going to be successful. It doesn't matter where you are.

Mrs. MORELLA. Except stress will also be a very important ingredient, would it not?

Dr. LENFANT. That is correct, to the extent that stress may make you eat more, or drink more, or less, or whatever, how you respond.

Mrs. MORELLA. You see diet as more important, then?

Dr. LENFANT. Well that diet is a complex thing. That is why we have such problems with compliance with regard to cholesterol control, or weight, for that matter. It is a very difficult thing to control.

Mrs. MORELLA. Then in terms of the number of measurements that you would need to be able to determine the lowering of cholesterol, is there a number?

Dr. LENFANT. Well the minimum which is recommended in all the documentations which are issued by the National Cholesterol Education Program is 2.

However, I can assure you that in many instances it will be more than 2. And if the cholesterol is high today, physicians and specialists will look at what we call the sub-fraction of the total cholesterol. By "sub-fraction," you know, cholesterol is kind of an envelope for all kind of different sorts of lipids which are genetically determined. Today that is what you are looking at before starting a treatment, if you have to follow a very serious, substantial treatment.

Mrs. MORELLA. Did you want to comment on that, Mr. Chan?

Mr. CHAN. I would agree that the program itself suggests the two-step diet. They have some estimate in terms of what they can achieve, you know, like 5 to 7 percent versus 8 to 14 percent in reduction.

But the reason is that in a survey in 1990 a physician suggested that half of them said, you know, only about one-third of the patients stay on the diet and it was effective in that way. So in one way the strategy is a good one; in another way it is difficult to implement.

Mrs. MORELLA. Mr. Tanner wanted to follow up on that.

Mr. TANNER. Talking about compliance, I had a friend at home whose name was Coach Wallace. He died at age 78 and he weighed 419 when he checked into the hospital on his last illness.

Somebody asked him one time, said, Coach, why don't you take off some of that weight?

He said, Son, if it was as much fun taking it off as it was putting it on, I'd do it.

[Laughter.]

Mr. TANNER. I just had one other question.

We were talking about the Guidelines that the NCEP is going to issue. What is the time line on that, Doctor? Do you know?

Dr. LENFANT. I think they should come within the next few months. I would say it would be three, four, five months, something of that sort. They are very carefully reviewed at this time.

Our process to get those things published is a little bit slow sometimes, but we are working on it.

Mr. TANNER. We would like to be kept apprised of that.

Dr. LENFANT. Yes.

One thing, Madam Chairwoman, that I really would like to underscore one more time is that—and that relates to I think what Mr. Tanner was saying earlier—the decision to start a treatment, whether dietary or pharmacological, is not based—the good practice of medicine would dictate that it should not be based on one measurement of cholesterol. It should be several measurements, and you should look at the person.

Is there a family of heart disease?

Has that person high blood pressure?

Is that person a heavy smoker?

Is that person 50 pounds overweight?

Is that person with diabetes?

All these things come into the decision-making. The guidelines are not a single measurement, but a prescription. The prescription will result from looking at the whole thing, the entire situation and all the determinants and risk factors in these patients.

Mrs. MORELLA. I would like to recognize now another Member of the subcommittee, Mr. Gutknecht, for any questions he may have.

Mr. GUTKNECHT. Thank you, Madam Chair.

I hope this question is not redundant. I apologize because I have had several other events going on at the same time, but I would almost like to get back to some rather basic issues. To me, I am not really clear on the various forms of what is loosely described as "heart disease."

I am wondering if you could share with me what you mean when you say "heart disease," any one of the panelists who might want to talk about that.

Then secondly, I want to get down to what exactly a "heart attack" is and what role cholesterol actually plays in the various forms. I wonder if you could share some of those things with me.

Dr. LENFANT. Yes. If I have used the word "heart disease," that was an error. By "heart disease" we really include all the elements that can affect the heart as an organ.

Now when it comes to cholesterol, we are talking about the process which is known as arteriosclerosis. Now arteriosclerosis can affect any artery in the body, but the coronary arteries, which are the arteries providing blood supply to the heart—to the tissue, so that the pumps, if you want, can function properly, are very prone to arteriosclerosis.

What it is, it is a deposit of fatty tissue into the lumen of these arteries that eventually leads to the obstructions. When they are obstructed, it is just like it would keep you from breathing. You keep the heart from breathing, to receiving oxygen, nutrients for the heart to function properly, and that leads to a heart attack, which is a very sudden process.

When it happens, you really have to do something to provide back some oxygen and other nutrients to the heart tissue. Basically what you have to do is to remove the obstruction which has occurred.

Often the obstruction, the completion, if you want, the complete closure is not the result of the fatty tissues which are obstructing, or reducing the diameter of the arteries, but because of these fatty tissues the blood does not circulate as freely as it would if the vessel was up, and you have a coagulation of the blood where this fatty tissue, this plaque as it is called, are.

It is a sudden coagulation of the blood, the formation of a blood clot, which results in a sudden heart attack. Did I answer your question?

Mr. GUTKNECHT. Yes, but I'm still—as I understand it—and a little knowledge is a dangerous thing, so I want to see if I can get to the bottom of this. Do you know the difference between an embolism and a thrombosis?

Could you explain that to me?

Dr. LENFANT. You are talking about the same thing, except that the embolisms, the blood clots, are formed somewhere and travel somewhere else.

A thrombosis is the formation of the blood clot itself. For example, take the case of Mr. Quayle. As I understand his story, he had a blood clot in his leg, and it traveled to his lung and obstructed the blood vessel in his lungs.

But the thrombosis occurred in the leg.

Do you see the distinction?

Mr. GUTKNECHT. Yes.

Madam Chairman, can I pursue this just a little bit more?

Mrs. MORELLA. Certainly.

Mr. GUTKNECHT. I am learning more and more about the technologies because I have some friends back in Rochester who are involved in some of these things. As I say, I am embarrassed to expose all my ignorance here in front of the committee, but why is it when we talk about heart disease if you talk about pacemakers and some of the other technology that is available today, how is that related to heart disease?

Dr. LENFANT. Well, the pacemaker— for the heart to function properly to send blood to all of your tissues, your brain, your legs, whatever, wherever on your body, it has to beat in a regular fashion. It is clockwork. It has to be very regular.

The number of heartbeats would increase if you go up and down the stairs, but also it has to be regular.

In many instances, often as a consequence of repeated heart attack, you may have a disruption in the regularity of the heart beats and therefore the heart functions in a somewhat asynchronic fashion.

What the pacemaker would do, it is a device that you insert in order to re-establish the regularity of the heartbeat.

Did I answer your question?

Mr. GUTKNECHT. More or less.

Is it possible, then, to have a heart attack and still have very low cholesterol?

I ask the question, and we are all products of our own environment, and our background and the people we know. A good friend of mine who died of a heart attack at a very young age was in perfect physical condition and had a very low cholesterol rate.

I have always questioned what the real relationship is between heart disease, and irregular heartbeat, and cholesterol, and plaque, and all these other things. I have never completely understood all that, and I still do not understand why someone in relatively per-

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fect health—in fact, he was a phys ed instructor and had low cholesterol—and yet he died of a heart attack.

Dr. LENFANT. My guess is that your friend died of "sudden death." Sudden death can result from two things. It can be a true "heart attack," as I have described it; or it can be a disruption in the conduction of the nerve signals into the heart which can be congenital. It can be due to scar tissue. It can be due to whatever you want. Or drugs. And that would cause a sudden death without a heart attack.

A heart attack is very defined as a sudden obstruction of the coronary vessel, the coronary artery.

Mr. GUTKNECHT. Finally, Madam Chair, and I do want to ask one last question relating to strokes, and what level cholesterol plays in strokes.

Dr. LENFANT. It does. As a matter of fact, another artery, or other arteries which are very prone to arteriosclerosis are the carotid arteries, which are the ones bringing the blood into your brain.

These arteries quite often lead to an obstruction because of the arteriosclerotic process and becomes the site of a blood clot formation. That blood clot may move from the neck up to your brain and cause a stroke.

Mr. GUTKNECHT. Thank you, Madam Chair.

Mrs. MORELLA. Thank you very much, Mr. Gutknecht.

Dr. Lenfant, as we finish up, do you not think physicians need to make sure that they are explaining to their patients what this GAO report has pointed out, and what you in your own way have kind of confirmed?

Should they not—do they explain to their patients what cholesterol testing tells us?

Dr. LENFANT. I personally believe that the physicians have a responsibility to describe indeed the problems that may exist—and I use purposely "may exist"—with measurements. But again, I think that the decision that a physician is going to make relative to a patient is most likely not based exclusively on that.

So it is important to explain that, but it has got to be done in a way such that the patient does not focus exclusively on that thing and ignore the other elements which are going to be part of the decision-making.

Mrs. MORELLA. And that would be part of what would have to be explained, I would think.

Dr. LENFANT. Sure. Absolutely.

Mrs. MORELLA. I think that is what is important, really, and probably should be in the curricula at medical schools.

Dr. LENFANT. Oh, "medical education" is an entirely different issue. There are lots of things which should be in medical educations—

[Laughter.]

Dr. LENFANT. —but I would like to say that, for example, in the Guidelines, a copy of which is here, and that is the Executive Summary, they do talk about those things and the need to have more than one blood measurement, blood cholesterol measurement.

Likewise, here is a brochure for the public, the title of which is "So You Have High Blood Cholesterol" And in there it tells you how to deal with that situation and what to make of it if the physician would tell you you do have high cholesterol.

Mrs. MORELLA. I would like to just finally ask Mr. Chan, were you surprised by the findings of the GAO report? Would you like to characterize how you and GAO responded to what you discovered?

Did you think that cholesterol testing was accurate and valid and all before you started?

Mr. CHAN. Yes. In fact, I must say I thought that, you know, often we think technology can do a lot better than what we think it actually is doing. So I think the reality was that, one, that the so- called instrumentation side of it still gives you a lot of variability, which is surprising to me.

Another thing I really learned from this study is the biological side, the clinical end, which is something that I was not aware of before I started this study, the wide variability of that.

And in a way it does suggest that when you do take the test, make sure, you know, you should be fasting, you should do all the right things and take your test so you will get a relatively accurate measure in terms of minimizing the biological variations.

I think the other end that is on our mind, as Mr. Tanner asked, is whether we—you know, we did not have any recommendations, but the question really is, to what degree can we find out the way physicians practice in terms of, one, are they aware of the variations, of why they are?

While we are saying that you should not take just one test and make a decision on it, I would also say that from a statistical point of view that if the variation is 16 percent, plus or minus around that number, taking another test only reduces it down to 12 percent. If you take another test, it is down to 10 percent.

So it is still a pretty wide variation around that as you average, and that is the nature of statistics, unfortunately.

I guess you have been pursuing the question of to what degree can we best educate the public and physicians. I certainly believe that this hearing will highlight the need for a public awareness a lot more.

Mrs. MORELLA. Do you also note that people are spending I think, what is it, an average of like $1000 a year on medications to lower their cholesterol?

Do you think that many of those people, or some of those people do not need those drugs? And maybe there are others who do who do not have it?

I mean, can you see that consequence, too?

Mr. CHAN. Yes. And unfortunately, we do not have the data to understand it better.

But I think I would answer it in a different way that, based on the 1990 Survey from NIH, I think over 50 percent of the physicians said that the current emphasis on cholesterol was producing needless anxiety in their patients, which is a very interesting finding from my perspective anyway. Maybe to understand these variations could reduce these anxieties.

Mrs. MORELLA. I would think it could.

Dr. LENFANT. Could I comment on that?

Mrs. MORELLA. Yes, indeed, Dr. Lenfant.

Dr. LENFANT. First of all, a dietary treatment does not really cost very much. Now the pharmacological treatment, physicians have a choice between several classes of drug. Only one of them is relatively expensive, and that is a class which is called the Statins, Mevacor, and Simvastatin, and what have you.

The treatments may go from $700 to $800 a year, but that is a very small number of patients taking this drug. It is approximately 1.2 million people out of the 5- to 5.5 million people who are taking a pharmacological treatment.

All the others are really following a dietary treatment, more or less. We wish it would be better, but at least they are trying to do well with their dietary treatments.

Mrs. MORELLA. So I think we have learned a great deal from this hearing. It is like Frost describing a poem when he said. It tells me something I didn't know I knew, and that is the common sense of making sure that you are aware of the range, the variability, the other forces that enter into what may make your cholesterol high, low, borderline, and have the treatment—and have many measurements, and make sure the measurements are accurate so that we can make sure that, what is it we say, "this is our heart, and we want to keep it."

So if there are no further questions then from other Members of the subcommittee, we will now adjourn this Valentine's Day hearing.

Thank you very much, Dr. Lenfant, Mr. Chan, and Mr. Oppenheim.

Dr. LENFANT. Thank you.

Mr. CHAN. Thank you.

Mr. OPPENHEIM. Thank you, very much.

[Whereupon, at 3:20 p.m., the hearing was adjourned.]

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